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HYPOCHROMIC ANEMIA OF INFANTS

COMPARISON OF THE EFFICACY OF FERRIC AND OF FERROUS IRON

RUTH STEPHENSON, M.D.

PHILADELPHIA

The study reported here was undertaken to determine whether hypochromic anemia is common in so-called normal infants between 3 months and 2 years of age and to determine the form of iron, size of dose and duration of therapy most effective in correcting the condition.

SURVEY OF THE LITERATURE

That normal infants and children exhibit lower hemoglobin values than do normal men or women has long been clear. The drop from the excessively high hemoglobin level of the normal newborn infant to this hypochromic level has been demonstrated by numerous competent investigators.[1] While the reduction in hemoglobin suffered by newborn infants through the first six weeks of life may fairly be termed physiologic, as it is due to intrinsic factors, from the sixth week forward the hypochromia is nonphysiologic, since it is influenced by extrinsic factors such as exposure to infection, artificial or breast feeding or

From the Newborn Service, Philadelphia General Hospital, and the Children's Hospital.

1. (*a*) Drucker, P.: Investigations on the Normal Value for the Hemoglobin and Cell Volume in the Small Child, Acta pædiat. **3**:1, 1924. (*b*) MacKay, H. M. M.: The Normal Hemoglobin Level During the First Year of Life, Arch. Dis. Childhood **8**:221, 1933. (*c*) Kato, K., and Emery, O. J.: Hemoglobin Content of the Blood in Infancy, Folia haemat. **49**:106, 1933. (*d*) Elvehjem, C. A.; Peterson, W. H., and Mendenhall, D. R.: Hemoglobin Content of the Blood of Infants, Am. J. Dis. Child. **46**:105 (July) 1933. (*e*) Merritt, K. K., and Davidson, L. T.: The Blood During the First Year of Life, ibid. **47**:261 (Feb.) 1934. (*f*) Osgood, E. E., and Baker, R. L.: Erythrocyte, Hemoglobin, Cell Volume and Color Volume and Saturation Index Standards for Normal Children of School Age, ibid. **50**:343 (Aug.) 1935. (*g*) Mugrage, E. R., and Andresen, M. I.: Values for Red Blood Cells of Average Infants and Children, ibid. **51**:775 (April) 1936. (*h*) Faxén, N.: The Red Blood Picture in Healthy Infants, Acta pædiat. (supp. 1) **19**:11, 1937.

administration of iron. Josephs [2] made this clear in his recent excellent monograph. He showed that iron deficiency plays no part in the causation of anemia in the first six weeks of life and only rarely is a factor in the first three months. However, he pointed out [3] that by the end of the sixth month there is a relative exhaustion of those stores of iron present in the body at birth or deposited as a consequence of the breakdown of hemoglobin that occurs during or shortly after birth.

The anemia which follows this depletion of stored iron in the rapidly growing infant and which is reflected in his blood picture by the age of 3 or 4 months is literally one of the nutritional anemias. Yet because it is usual it is often regarded as normal for this age, and it is commonly expected to cure itself later, when egg, spinach and finally a full mixed diet is given. Indeed, anemia in this age period may be unrecognized. This was stressed recently by Guest and Brown,[4] who after accurately determining the size and hemoglobin content of the erythrocytes of infants between 6 months and 2½ years of age stated that ". . . borderline anemia has been demonstrated to occur much more frequently among seemingly normal infants than is generally recognized by most pediatricians."

Clinically, the concept is old that iron deficiency is the chief cause of low production of hemoglobin, whether in adults or in children. Recovery from hypochromic anemia after administration of adequate amounts of iron has long supported this concept. In the field of pediatrics it was given fresh confirmation when MacKay [5] demonstrated that babies of mothers who had received iron during pregnancy showed higher hemoglobin values than the babies of untreated mothers.

That the hypochromia present in infants from 3 or 4 months through at least 2 years of age does not accompany optimal health is suggested by MacKay's finding,[6] in a study of artificially fed infants of the type ordinarily found in an infant welfare center, that even a slight degree of anemia was sufficient to lower markedly their resistance to disease.

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2. Josephs, H. W.: Anemia of Infancy and Early Childhood, Medicine **15**: 307 (Sept.) 1936.

3. Josephs, H. W.: Iron Metabolism, Bull. Johns Hopkins Hosp. **55**:259, 1934.

4. Guest, G. M., and Brown, E. W.: Erythrocytes and Hemoglobin of the Blood in Infancy and in Childhood, Am. J. Dis. Child. **52**:616 (Sept.) 1936.

5. MacKay, H. M. M., and Goodfellow, L.: Anemia of Infancy—Iron Deficiency, Medical Research Council, Special Report Series, no. 157, London, His Majesty's Stationery Office, 1931.

6. MacKay, H. M. M.: Anemia in Infancy and Childhood, Practitioner **134**: 200, 1935.

It has more recently been recognized [7] that blood-building factors other than iron may also be deficient in cases of so-called iron deficiency anemia. One cannot exclude the possible supplemental effect of vitamin C, yeast, liver, the pyrrole ring, cobalt, etc., on the synthesis of hemoglobin. The need of a copper supplement in the infant dietary has been much disputed. Josephs,[8] Bloxsom,[9] Cason,[10] and Elvehjem and others [11] were early proponents of its use in treating anemia of infants. More recently Josephs [2] concluded that its action ". . . consists in aiding the formation of a hemoglobin, probably as a catalyst." He added: "Copper is rarely necessary for complete recovery but may be useful in accelerating recovery." In this connection, while admitting that it may be necessary in rare cases to add copper in treatment before a complete cure is obtained, Parsons [12] pointed out that the necessity for using copper hardly exists because all commercial iron salts contain copper as an impurity. Further, it has been said that it is not difficult to create serious copper poisoning by administering relatively small amounts of copper.[7b]

The general subject of iron metabolism has been widely investigated within the past decade, first by Europeans led by Starkenstein.[13] Shortly thereafter Lintzel [14] published the results of his many researches, together with a valuable summary of the world literature on iron metabolism. Since then the benefit of treating hypochromic anemias by iron has been repeatedly demonstrated.[15]

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7. (*a*) Josephs.[2] (*b*) Minot, G. R.: The Anemias of Nutritional Deficiency, J. A. M. A. **105**:1176 (Oct. 12) 1935.

8. Josephs, H. W.: Treatment of Anemia of Infancy with Iron and Copper, Bull. Johns Hopkins Hosp. **49**:246, 1931.

9. Bloxsom, A. P.: Copper and Iron Requirements in Infancy, South. M. J. **25**:401, 1932.

10. Cason, J. F.: Use of Copper and Iron in Treatment of Secondary Anemia in Children, J. Pediat. **4**:615, 1934.

11. Elvehjem, C. A.; Siemers, A., and Mendenhall, D. R.: Effect of Iron and Copper Therapy on the Hemoglobin Content of the Blood of Infants, Am. J. Dis. Child. **50**:28 (July) 1935.

12. Parsons, L. G.: The Treatment of Nutritional Anemia in Infants, Brit. M. J. **1**:1009 (May 16) 1936.

13. Starkenstein, E., and Weden, H.: Ueber das anorganische Eisen des Organismus, Arch. f. exper. Path. u. Pharmakol. **134**:274, 1928.

14. Lintzel, W.: Neuere Ergebnisse der Erforschung des Eisenstoffwechsels, Ergebn. d. Physiol. **31**:844, 1931.

15. (*a*) Josephs.[8] (*b*) Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing Acidity of Gastroduodenal Contents in Certain Cases of Anemia, Am. J. M. Sc. **181**:25, 1931. (*c*) Heath, C. W.; Strauss, M. B., and Castle, W. B.: Parenteral Administration of Iron, J. Clin. Investigation **11**:1293, 1932. (*d*) Elvehjem, C. A.: Relative Value of Inorganic and Organic Iron in Hemoglobin Formation, J. A. M. A. **98**:1047 (March 26) 1932. (*e*) Davidson, L. S. P., and others: Nutrition in Relation to Anemia, Brit.

(Footnote continued on next page)

In recent years attention has focused on determination of the form in which iron is best given. From a study of the literature it appears that the ideal form of iron in therapy of infants should meet the following criteria:

1. It should be given orally. Apart from the factors of discomfort and expense, Heath, Strauss and Castle [15e] have shown that adequate doses of iron are toxic when administered parenterally.

2. It should be inorganic, since it appears that all iron compounds must be broken down into inorganic salts before the iron can be assimilated.[16]

3. It should be in solution, because the possible deficiency of gastric acidity in an infant might make the solid form nonavailable.[17]

4. It should be in ferrous form. Experimental work indicates that ferric iron after reaching the stomach either reacts with proteins to form precipitates which cannot be absorbed or is reduced to a ferrous compound which can then be absorbed from the intestines. Further, increasing clinical data derived from treatment, especially of adults, attests to the superiority of ferrous over ferric iron.[18]

There are a few reports of treatment of hypochromic anemia with iron or a combination of iron and copper within the limited age range of from 3 months to 2 years.[19] However, no controlled study comparing

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M. J. **1**:685, 1933. (*f*) Heath, C. W.: Oral Administration of Iron in Hypochromic Anemia, Arch. Int. Med. **51**:459 (March) 1933. (*g*) Dameshek, W.: Primary Hypochromic Anemia: Hypoferrism III, West Virginia M. J. **30**:193, 1934. (*h*) Parsons, L. G., and Smallwood, W. C.: Anemias of Infancy and Childhood, Practitioner **134**:298, 1935. (*i*) Toland, O. J.: Incidence and Treatment of Secondary Anemia in Out-Patient Maternity Patients, Am. J. Obst. & Gynec. **31**:640, 1936.

16. Starkenstein and Weden.[13] Elvehjem.[15d]

17. Mettier and Minot.[15b] Josephs.[2]

18. (*a*) Reimann, F., and Fritsch, F.: Eisenverbindungen bei den sekundären Anämien, Ztschr. f. klin. Med. **115**:13, 1930. (*b*) Witts, L. J.; Davies, D. T., and MacKay, H. M. M.: Therapeutic Use of Iron, Proc. Roy. Soc. Med. (Sect. Therap. & Pharm.) **24**:7, 1931. (*c*) Parsons, L. G.: Anemias of Infancy and Childhood, Arch. Dis. Childhood **8**:85, 1933. (*d*) Davidson, L. S. P.: Idiopathic, Hypochromic Anemia, Proc. Roy. Soc. Med. **26**:607 (March) 1933. (*e*) Lottrup, M. C.: Treatment of Anemia in Children, Am. J. Dis. Child. **47**:1 (Jan.) 1934. (*f*) Fullerton, H. W.: Treatment of Hypochromic Anemia with Soluble Ferrous Salts, Edinburgh M. J. **41**:99, 1934. (*g*) Fürth, O., and Scholl, R.: Absorption of Ferrous and Ferric Compounds, J. Pharmacol. & Exper. Therap. **58**:14 (Sept.) 1936. (*h*) Lucas, G. H. W, and Henderson, V. E.: On the Administration of Iron, Canad. M. A. J. **34**:53 (Jan.) 1936. (*i*) Starkenstein and Weden.[13] (*j*) Heath.[15f]

19. MacKay, H. M. M.: Copper in Treatment of Nutritional Anemia, Arch. Dis. Childhood **8**:145, 1933. Hawksley, J. C.; Lightwood, R., and Bailey U. M.: Iron-Deficiency Anemia in Children, ibid. **9**:359, 1934. Josephs.[3] Guest and Brown.[4] Bloxsom.[9] Elvehjem, Siemers and Mendenhall.[11] Parsons.[12] Parsons and Smallwood.[15h]

the efficacy of ferric with ferrous iron in treating infants of this age is known. On this matter Josephs [2] reported in September 1936:

> Recent work indicates that ferrous iron is of greater value than ferric and may exert its maximum effect with a smaller dosage. The greater value of ferrous iron has not yet been demonstrated in anemia in infancy. It is not enough merely to treat two series of infants and compare rates of recovery statistically; it must be shown that a maximum effect may be obtained by a smaller dose.

The present investigation, though unpublished, had been completed at that time and met the specifications Josephs later mentioned.

Opinions of authorities on proper doses of ferrous and ferric iron have been widely divergent, even in the subject of treatment of adults showing hypochromic anemia.[20] Thus Witts [21] stated that a patient took 300 grains (19.4 Gm.) of iron and ammonium citrates daily "with impunity," and added, ". . . . while higher dosage than necessary is unwise, there is no excuse for giving too little. . . . There now seems no doubt that the effective dosage of preparations of iron is directly proportional to the ease with which they yield ferrous ions." He expressed the opinion that the most important facts derived from recent work on iron are the futility of injecting iron and the safety of giving large doses by mouth. At the other extreme, Deobald and Elvehjem,[22] reasoning from their results in feeding high amounts of iron and aluminum salts to chicks, urged that precautions be taken against high ingestion of iron by either infants or adults.

Workers among children likewise vary in their recommendations.[23]

Nor is there agreement as to the best dose of iron for infants under 2 years of age.[24] The different doses recommended by various investigators are summarized in table 1.

Definite knowledge is scant as to the daily iron intake necessary to maintain an optimal hemoglobin level in infants from 3 months to 2 years of age. For older children the iron requirement has been estimated [25] at 0.76 mg. per hundred calories of food ingested. Jeans,[26] reporting on balance experiments, concluded that babies need more iron

20. Brock, J. F.: Relation Between Hypochromic Anemias and Iron Deficiency, Brit. M. J. **1**:314, 1937. Heath.[15f]

21. Witts, L. J.: Therapeutic Action of Iron, Lancet **1**:1 (Jan. 4) 1936.

22. Deobald, H. J., and Elvehjem, C. A.: Effect of Feeding High Amounts of Soluble Iron and Aluminum Salts, Am. J. Physiol. **111**:118 (Feb.) 1935.

23. Goldstein, H.: Use of Iron and Iron Catalysts in Simple Anemia of Children, Arch. Pediat. **52**:234 (April) 1935. Ascham, L.: Study of Iron Metabolism with Preschool Children, J. Nutrition **10**:337 (Sept.) 1935.

24. Usher, S. J.; MacDermot, P. N., and Lozinski, E.: Prophylaxis of Simple Anemia in Infancy with Iron and Copper, Am. J. Dis. Child. **49**:642 (March) 1935.

25. Growth and Development of the Child: III. Nutrition, White House Conference on Child Health and Protection, New York, Century Company, 1932.

26. Jeans, P. C.: Specific Factors in Nutrition, J. Pediat. **9**:695 (Nov.) 1936.

than most of them get and recommended a daily supplement of from 7.5 to 10 mg. for those up to 1 year of age. He added that more than this amount is unnecessary and that amounts greatly in excess are likely to be definitely harmful. Franklin [27] watched hemoglobin increases in infants with hypochromic anemia given iron therapy for at least nine weeks. Ross and Summerfeldt [28] used various forms of iron therapy during nineteen consecutive months in studying normal children aged 5 to 14 years and found that maintaining the total daily intake of iron at 36 mg. for five months caused progressive rises in hemoglobin.

TABLE 1.—*Doses of Ferric and of Ferrous Iron Used by Various Investigators*

Authors	Subjects	Medication	Comment
Heath, Strauss and Castle [15c]	Adults	Iron and ammonium citrates containing 1,000 mg. metallic iron, daily	Occasionally 2,000 mg. necessary for response
Reimann and Fritsch [18a]	Adults	Ferrous chloride, containing as little as 22-100 mg. metallic iron, daily	
Davidson [18d]	Adults	Iron and ammonium citrates 90 gr. (5.85 Gm.) or ferrous chloride 5-7½ gr. (0.32-0.49 Gm.)	Comparable result
MacKay [6]	Children, 4 mo.-4 yr.	Iron and ammonium citrates 9-15 gr. (0.58-0.97 Gm.) or ferrous sulfate 4½ gr. (6.29 Gm.)	Daily, in treatment
	Infants, 2-18 mo.	Iron and ammonium citrates 4½ gr. (0.29 Gm.) daily	In prophylaxis
Josephs [8]	Infants, 3-24 mo.	Iron and ammonium citrates 10%, 2 cc. per Kg. body weight, with added copper	
Parsons [12]	Infants	Ferrous sulfate 4 gr. (0.26 Gm.) three times a day or iron and ammonium citrates 4 gr. (0.26 Gm.) three times a day or reduced iron 1 gr. (0.06 Gm.) three times a day	Ferrous sulfate the most efficacious
Franklin [27]	3 infants, aged 8, 16 and 24 mo.	Iron and ammonium citrates in doses ranging from 30-60 gr. (1.94-3.88 Gm.) daily	Responses illustrate need for large doses
Guest and Brown [4]	Infants	Iron and ammonium citrates 12%, 0.5 cc. per Kg. body weight daily	
Merritt and Davidson [16]	Premature infants	Iron and ammonium citrates 0.3 Gm. per Kg. body weight daily	

It appears, then, that the literature lacks experimental data to clear these two questions: How much supplemental iron should be given daily to maintain an optimum hemoglobin level in the age range of from 3 months to 2 years; and how long should such doses be maintained?

SCOPE OF THE PRESENT STUDY

Since other investigators have shown that infants between 3 months and 2 years of age have average hemoglobin values appreciably lower than those of adolescents or adults, and since such hypochromia is

27. Franklin, A. W.: Anemia in Infancy, St. Barth. Hosp. Rep. **67**:103, 1934.

28. Ross, J. R., and Summerfeldt, P.: Hemoglobin of Normal Children, and Certain Factors Influencing Its Formation, Canad. M. A. J. **34**:155 (Feb.) 1936.

chiefly consequent on iron deficiency, this study was designed to learn (1) whether all healthy infants of this age range who live under good conditions exhibit the reported hypochromia; (2) how far adequate iron therapy raises their hemoglobin level; (3) the comparative efficacy of varying doses of ferric and ferrous forms of iron, and (4) for what length of time a maintenance dose of supplemental iron is indicated.

Critics have elsewhere made the point that the discrepancies between the absolute values of infants' hemoglobin reported by different careful observers must be partly due to variations in the living conditions and in the diet of the infants studied. Thus Faxén reported on infants in Göteborg none of whom was completely weaned before the age of 9½ months, whereas MacKay's material was taken from a center for well babies in London's East End. In this country likewise, most of the infants whose hemoglobin level was reported have been outpatients attending child health centers and consequently having diverse home environments.

In order that all subjects in this controlled study might have the same living and dietary conditions, a well run orphanage was chosen. While the infants did not, of course, have the individual care and the isolation from infection of the upper respiratory tract which often surround the child of well-to-do parents, their regimen of living and eating was directed by a staff of pediatricians and they received excellent nursing care. They were entirely comparable to the healthy, artificially fed babies seen in an ordinary city practice. Further, these institutionalized infants furnished controlled material for study, with no variable except the difference in the forms of iron medication administered. And, unlike floating outpatients, they received their iron therapy with regularity.

The infants selected were 64 healthy white boys and girls, American born, chiefly of Irish or of Italian parentage, with the age and sex distribution shown in table 2. They were in residence under uniform living conditions at St. Vincent's Hospital for Women and Children,[29] having been either born there or admitted as orphans when extremely young. Consequently, few had had the benefit of breast milk beyond the neonatal period. No premature infants or twins were included in the group. The few babies in whom illnesses subsequently developed which were serious enough to be reflected in failure to gain weight between two successive samplings of blood (four weeks apart) were dropped from the study. The chief factor, however, in reducing the number of infants from the original 64 to a total of 44 babies at the end of six months of study was the withdrawal of many for adoption.

In all cases the initial state of an infant's blood was established by at least two studies before therapy was started. The effect of therapy was checked by

29. This opportunity to study which of two forms of iron medication might prove the more helpful was extended through Dr. John A. McGlinn, Chief of Staff at St. Vincent's Hospital.

a like study every four weeks for three months, and the tests were repeated once more at the end of six months.

After the initial hemoglobin values had been well established, the assignment of these subjects to one or the other form of iron medication was made on the basis of age plus hemoglobin level. For example, for each baby of 7 months assigned to one form of iron a control aged about 7 months and with about the same hemoglobin level was assigned to the other form of iron. Unfortunately, over the course of three months unforeseen withdrawals reduced the number of these individual controls. Nevertheless, at the end of three months' treatment 30 infants given ferrous iron remained to serve as contrast for 27 who had had ferric iron.

In this study of the comparative efficacy of ferric and of ferrous iron in treating the hypochromic anemia of infants, the widely used and popular preparation of iron and ammonium citrates, in solution, was chosen as the ferric salt, contrasted with ferrous sulfate prepared as a sweetened elixir to increase its palatability and prevent its oxidizing to the ferric state.[30]

The decision as to what doses to use was, of necessity, arbitrary. As to iron and ammonium citrates, a middle course was sought between inadequate doses

TABLE 2.—*Age and Sex Distribution of Infants at the Beginning of the Study*

Age in Weeks	Boys	Girls	Age in Weeks	Boys	Girls
14-17	1	3	54-57	2	1
18-21	2	1	58-61	1	2
22-25	2	3	62-65	0	2
26-29	3	2	66-69	2	3
30-33	2	2	70-73	1	2
34-37	3	1	74-77	2	2
38-41	1	2	78-81	1	0
42-45	2	2	82-85	0	0
46-49	3	3	86-89	1	0
50-53	1	3			
Total				30	34

and excessive doses, which sometimes result in gastric irritation. Accordingly, each midafternoon 30 grains (1.94 Gm.) of iron and ammonium citrates was given to each baby in the first group, regardless of individual size; this was administered in 3 fluidrachms (11 cc.) of a 16⅔ per cent solution masked in 2 ounces (59 cc.) of orange juice. Thirty grains of iron and ammonium citrates represents approximately 340 mg. of metallic iron. To each baby in the second group 6 grains (0.39 Gm.) of ferrous sulfate was given in solution, likewise masked in 2 ounces of orange juice and administered each midafternoon. Six grains of ferrous sulfate represents approximately 78 mg. of metallic iron.

The doses of both these medications were decided on after a conference with Dr. Louis K. Diamond, who had tried them on a comparable age group and had obtained "satisfactory results with very little evidence of disturbance due to excessive dosage."[31] Diamond added: "I should assume that there is no fixed dose of iron for either adult or child which can be related to body weight, but that it depends upon the degree of anemia, the period of iron deprivation, and the amount absorbed in a given case."

30. The solution of ferrous sulfate was supplied by Smith, Kline & French Laboratories.

31. Personal communication.

In view of the controversy as to whether added copper is essential in the treatment of hypochromic anemia, the amount of copper contaminating these two iron salts was established. The preparation of iron and ammonium citrates chosen was the same that Merritt and Davidson [1e] used; the chemists who manufactured it stated that this salt, as previously analyzed, showed only 0.005 per cent of copper. Thus each baby given 30 grains of the salt received 0.1 mg. of copper daily. Similarly, the solution of ferrous sulfate employed was analyzed and found to contain 0.0357 mg. of copper per daily dose of 15 cc.[32] As Elvehjem,[11] after treating 55 babies ranging in age from 3 weeks to 1 year or over, recommended that 1.0 mg. of elemental copper be added to 25.0 mg. of elemental iron, it is evident that the two groups in this study received, as chance contaminants, only one tenth and one thirtieth, respectively, of the amount of copper he stated was essential for prompt and maximal response in hemoglobin level.

The duration of therapy for these normal infants was dictated by their response. While in the first month of treatment there were good gains in hemoglobin, further gains resulted from the second and third months' therapy. Even by the end of three months there was no evidence that a maximum hemoglobin level had been reached, and there was no certainty that iron supplemental to the food would be necessary to maintain the gains already made. Accordingly, at the end of three months' medication therapy was stopped for one group, while for the other group iron therapy was maintained to a total of six months. Final tests of the blood were then made for both groups. As the average hemoglobin levels of the two groups were nearly equal at the end of the first three months, it was felt that this further study should offer data for a fair comparison.

METHODS

Since the main characteristic of anemias due to iron deficiency is hypochromia and since response to iron therapy is reflected most strikingly in increase of hemoglobin, the essential measurement of blood change in these infants is that of hemoglobin. However, since microcytosis usually characterizes a hypochromic anemia,[33] red cell volumes were measured and routine red cell counts were made in addition (table 3).

I collected all specimens and carried out all estimations. The purpose was to make careful estimations by simple and yet well accredited methods in order that comparison between any two sets of readings

32. This analysis was made by Dr. D. L. Drabkin, of the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania.

33. Wintrobe, M. M.: Classification and Treatment of the Anemias on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Blood Cells, Arch. Int. Med. **54**:257 (Aug.) 1934.

might be valid; there was no intent to contribute to the already confusing data on the best clinical method of measuring hemoglobin.

Capillary blood flowing spontaneously from a deep prick of a finger tip was used. A sharp Hagedorn needle caused little trauma to the tissue. The finger sampled was held on a level with the heart, in order to reduce the factor due to differences in hydrostatic pressure. All collections were made during the middle of the morning, the time having a uniform relation to mealtime. The accuracy of the counting chamber and of all pipets was certified by the United States Bureau of Standards.

Tenth-normal hydrochloric acid was the diluent for the determination of hemoglobin, and the sample was required to stand at least an hour before being read. The Haden-Hauser hemoglobinometer, which is read directly in grams, was the

TABLE 3.—*Measurements on the Blood of Two Representative Subjects*

Age, Weeks	Weight, Lb.	R. B. C., Millions	Hemoglobin, Gm.	Volume Packed Red Cells, %	Mean Red Cell Volume, Cu. Microns	Hemoglobin Concentration, Gm. per 100 Cc.	Mean Hemoglobin Content per Cell, Micromicrograms
			Boy				
24	13.0	4.580	12.5	37	80	33.7	27.1
Ferric iron started							
28	13.5	4.970	12.5	34	68	36.7	25.0
32	13.9	5.330	13.5	39	74	34.6	25.4
36	14.4	5.390	14.2	39	74	36.4	26.3
Ferric iron stopped							
49	18.1	4.870	12.8	34	69	36.1	25.2
			Girl				
14	10.1	4.510	12.3	35	78	35.1	27.2
Ferrous iron started							
18	10.5	4.540	12.8	36	80	35.5	28.2
22	10.9	5.060	13.5	40	78	33.7	26.6
26	12.1	5.025	13.5	39	78	34.6	26.9
Ferrous iron continued							
39	15.0	5.070	14.5	36	71	40.3	28.4

colorimeter used, its mazda filter with a constant source of artificial light being chosen in preference to the varied brightness of light from the sky. Haden [34] found that readings made with this hemoglobinometer compare closely with those obtained by determining the oxygen capacity and the iron contents of the blood. In his laboratory, with this instrument, 100 per cent hemoglobin indicates 15.4 Gm. per hundred cubic centimeters of blood.

Hayem's solution was the diluent for the red cell count, and three minutes of vigorous shaking preceded each count.

To determine whether the red cells were altered in size during this course of treatment, mean red cell volumes were measured. Since any change in the diameter of a red cell is relatively small compared with its change in volume, the preferred measurement is that of volume. Numerous good methods of estimating cell volume are in common use, but most of them depend on having so large a

34. Haden, R. L.: Hemoglobin Standards, Am. J. Clin. Path. **3**:85, 1933.

sample that venous blood must be used.[35] This of course is not feasible when one is making frequent examinations of an infant. Accordingly, a modification of the known methods of estimating cell volumes in capillary blood was devised; this proved to be accurate to a gratifying degree. In brief, a few drops of blood from the pricked finger are collected in an extremely small glass cup previously prepared with enough heparin to prevent coagulation. The contents are mixed, the blood is drawn into three thin-walled capillary tubes of even bore, and both ends are sealed in flame to prevent leakage or evaporation. The blood is centrifuged until the cells are completely packed. The proportion of packed cells to the total blood column is then read with a hand lens against a good light.[36]

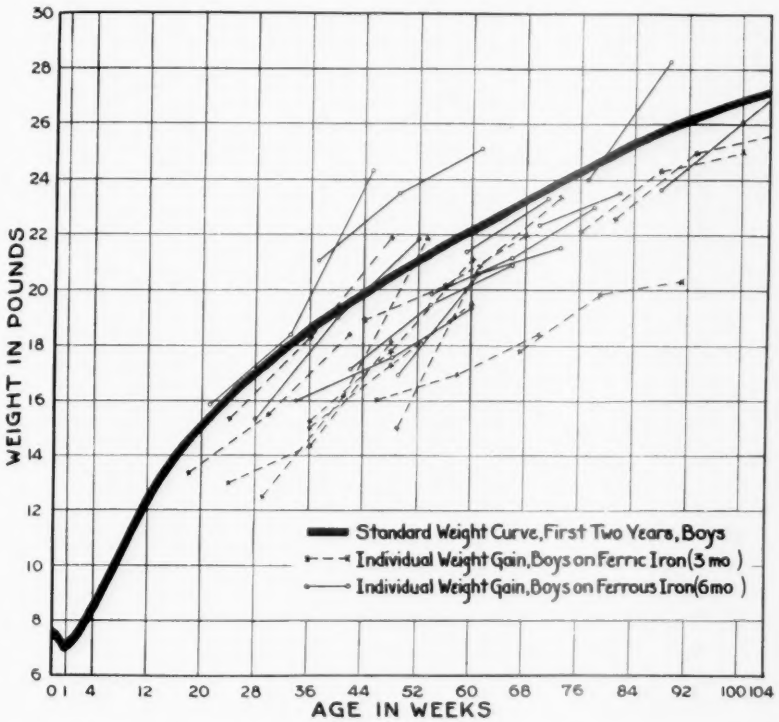
WEIGHT IN POUNDS
AGE IN WEEKS
Standard Weight Curve, First Two Years, Boys
Individual Weight Gain, Boys on Ferric Iron (3 mo.)
Individual Weight Gain, Boys on Ferrous Iron (6 mo.)

Chart 1.—Comparison of individual gains in weight (boys) with a standard curve.

The percentage of packed red cells to whole blood thus determined proved to be highly accurate. Often the three capillary tube readings per

35. Osgood and Baker.[1f] Wintrobe, M. M.: Volume and Hemoglobin Content of Red Blood Corpuscle: Simple Method of Calculation, Normal Findings and Value of Such Calculations in Anemias, Am. J. M. Sc. **177**:513, 1929. Haden, R. L.: Methods and Clinical Value of the Determination of the Size of the Red Blood Cell, ibid. **181**:597, 1931.

36. The details of this method and a statistical study of accumulated data on cell volume are to be reported later.

sample of blood checked each other exactly when percentages were computed, though blood was always deliberately drawn to varying levels in the three tubes. Indeed, the variation between the three readings seldom amounted to 1 per cent.

In contrast, the counting of red cells is notoriously inaccurate. Even when done with meticulous care, the variation in two successive counts due to technical error is large. Faxén [1h] quoted his mean error as 187,000 corpuscles. Berkson and others [37] reported that the standard

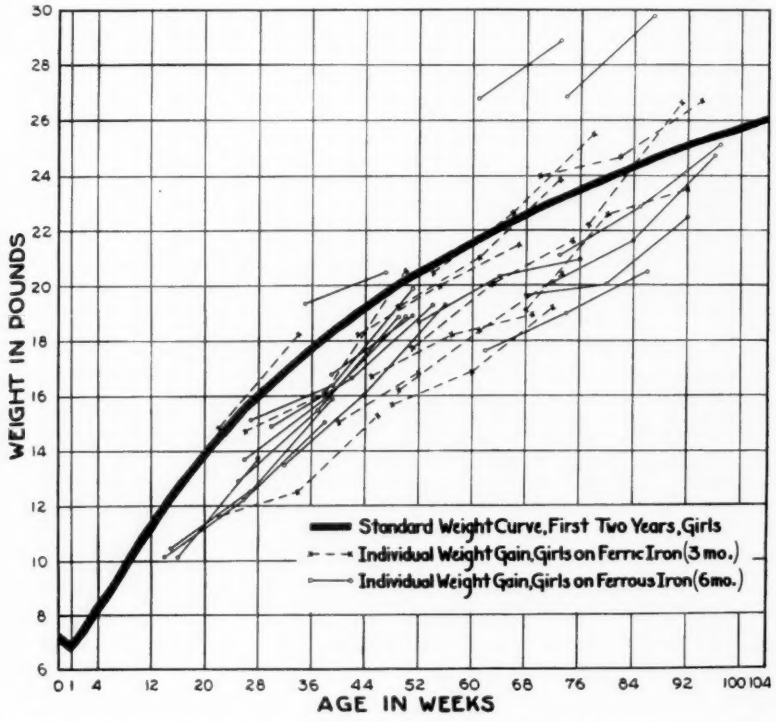
WEIGHT IN POUNDS
AGE IN WEEKS
Standard Weight Curve, First Two Years, Girls
Individual Weight Gain, Girls on Ferric Iron (3 mo.)
Individual Weight Gain, Girls on Ferrous Iron (6 mo.)

Chart 2.—Comparison of individual gains in weight (girls) with a standard curve.

deviation of the total count for a person with about 5,000,000 red cells per cubic millimeter is about 400,000. They therefore concluded that the estimate as usually made is significant within about 800,000 cells per cubic millimeter.

Since the estimation of mean cell volume in cubic microns is arrived at by dividing the percentage of packed red cells ($\times$ 10) by the red

37. Berkson, J.; Magath, T. B., and Hurn, M.: Laboratory Standard in Relation to Chance Fluctuations of the Erythrocyte Count as Estimated with the Hemocytometer, J. Am. Statist. A. **30**:414 (June) 1935.

cell count in millions, it would seem that the mean cell volume (quotient) must share in the inaccuracy of the red cell count (divisor). Hence variations in mean red cell volume arise as the result of inescapable technical error. For this reason, the extensive data collected on cell volumes in this study were not used as gages of the response of the anemias to iron therapy. Instead, this report will be limited to the effect of such therapy on hemoglobin alone.

RESULTS AND COMMENT

As gain in weight is one of the most acceptable gages of normal growth, the weights of these subjects before and during therapy were plotted against standard weight curves (charts 1 and 2). The standard curves were drawn from figures quoted in Holt and Howland's textbook of pediatrics [38] as representing the averages of more than 3,000 observations. In general, they indicate that boys throughout the first year are on the average one-half pound heavier than girls, and that by the end of the second year are a full pound heavier than girls. Of course, points falling considerably to either side of a standard weight curve may still lie within a normal range. At the beginning of observation a majority of these babies plainly weighed somewhat less than this arbitrary standard. Yet clinically they were not malnourished, and their subsequent weights during the period of observation (in most cases six months) indicate adequate gains. Possibly the body build of the numerous babies of Italian parentage would explain the frequent occurrence of low weights.

The relatively low hemoglobin values of these normal infants were unfailingly elevated by the use of a generous supplement of iron, as demonstrated in chart 3. While iron therapy also produced increases in the number and the volume of erythrocytes, rise in the hemoglobin level proved to be the most striking index of recovery from the moderate anemia common to these normal infants.

In order to show how the increasing hemoglobin values of these infants under therapy compare with average hemoglobin values of normal but untreated infants, they were plotted against a background of two curves reported by different investigators (chart 3). No one curve can be used as standard because in recent years numerous competent observers [1] have reported average hemoglobin curves of normal infants which differ rather sharply from each other as to absolute values. It is not clear why the values of one are consistently higher than those of another, except in the case of Faxén, of Sweden, who limited him-

38. Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners, New York, D. Appleton and Company, 1926.

self to breast-fed infants. Differences in technic and in race must also be contributory. Nevertheless, the *forms* of these numerous curves are strikingly similar. The two used as background for chart 3 were chosen because both deal with city-born American babies apparently otherwise comparable to those in the current study: the curve by Kato and Emery [1c] representing 780 normal white infants from birth to the age of 2 years, and that by Elvehjem [1d] representing 750 such infants from birth to 5 years.

Chart 3 suggests that 14 Gm. per hundred cubic centimeters of blood is the height to which the hemoglobin usually climbs under the

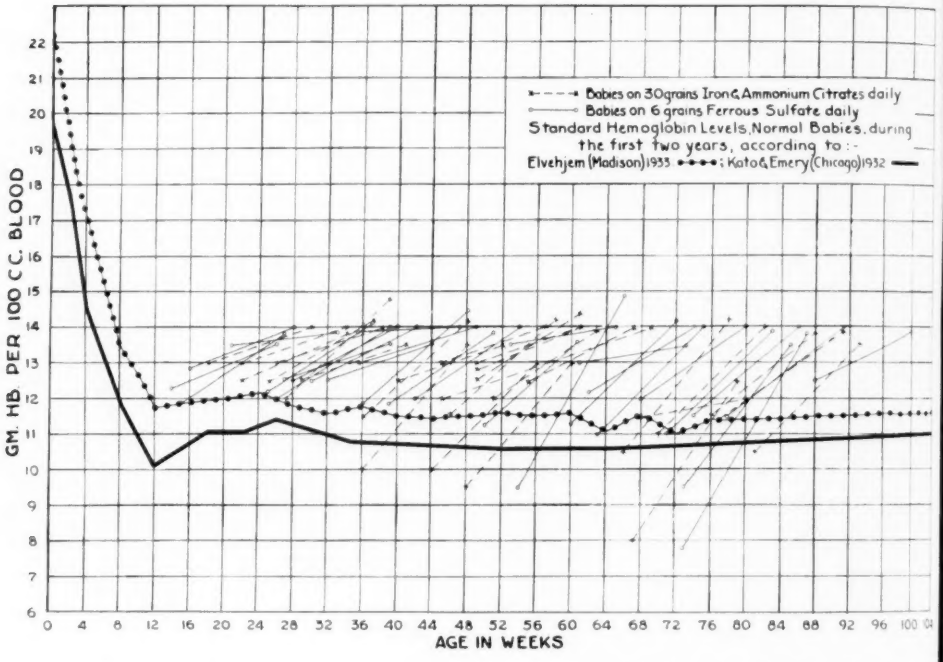
Babies on 30 grains Iron & Ammonium Citrates daily
Babies on 6 grains Ferrous Sulfate daily
Standard Hemoglobin Levels, Normal Babies, during the first two years, according to:-
Elvehjem (Madison) 1933; Kato & Emery (Chicago) 1932
GM. HB. PER 100 C.C. BLOOD
AGE IN WEEKS

Chart 3.—Increases in the hemoglobin of 57 normal babies during three months' treatment with supplemental iron, as compared with standard hemoglobin levels.

conditions of this study. This is roughly comparable to the 13.5 Gm. maximum (Newcomer method) at which Elvehjem and others [11] found that hemoglobin curves of infants flatten out after iron and copper therapy.

Individual gains in hemoglobin during three months' iron therapy, as illustrated in chart 3, suggest that the ferrous iron was fully as effective as the ferric, though its metallic iron content was only one-fifth that of the ferric. This proves to have been the case, as indicated in table 4, where the average hemoglobin levels of the two groups appear.

The graphic representation of these data in chart 4 suggests that ferrous iron in the doses used was a little more quickly effective than ferric—an impression expressed earlier by MacKay.

TABLE 4.—*Comparison of the Average Hemoglobin Levels of the Groups Given Ferric and Ferrous Iron*

	Babies on Ferric Iron, Average Hemoglobin in Grams	Babies on Ferrous Iron, Average Hemoglobin in Grams
Before any therapy	11.70	11.78
After 1 month's therapy	12.80	13.00
After 2 months' therapy	13.40	13.40
After 3 months' therapy	13.75	13.90
	Ferric iron stopped	Ferrous iron continued
After 3 additional months	13.50	14.10
Standard deviation	±0.75	±0.44

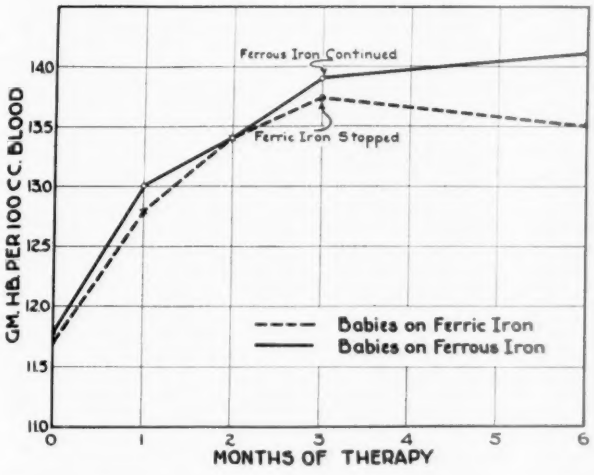

Chart 4.—Graphic representation of the comparison in table 4.

It is noted that the hemoglobin of 3 infants failed to reach the level of 13.5 Gm. in the three months of medication, and that these 3 infants all belonged to the group given ferric iron. This fact alone would not prove ferric iron less efficient than ferrous, as there may have been some unrecognized retarding factor in these few cases.

Copper must have been of little or no effect in evoking the hemoglobin increases shown in this study, since the traces of copper present in the ferric and ferrous compounds were only one tenth and one thirtieth, respectively, of the amounts Elvehjem found necessary to raise hemoglobin to his maximum of 13.5 Gm. This conclusion seems the

more clear when it is realized that the group of infants receiving ferrous iron, who were getting only one-third the trace of copper ingested daily by the ferric group, showed quite as good hemoglobin rises as the latter.

Gastrointestinal disturbances attributable to the medication were rare throughout this study, doubtless partially because treatment was begun so gradually that four or five days elapsed before the full dose of either medicament was administered daily. The few patients in whom diarrhea developed subsequently were in the group receiving iron and ammonium citrates, and the condition was easily controlled by a temporary reduction in dose. Some infants in each group resisted being given their daily medication; it was noted that these same infants had fought against receiving their orange juice, even when it included no iron.

Collateral effects of treatment which no chart can picture are the prompt improvement in color and disposition of both groups of babies while they were under treatment. Within the first month the palms of their hands and the soles of their feet had become so rosy as to attract the notice of lay ward attendants. At the same time their physical activity and well-being seemed increased. Though no precise record was kept, it was agreed that severe infections in the nursery were fewer than in previous years. This is interesting in view of the point MacKay [5] emphasized, namely, that anemia is so important a factor in predisposing to infection that no anemia, even of slight degree, is insignificant.

The advantage of giving a maintenance dose of iron, up to the age of 2 years at least, even after hemoglobin has been built up to an optimal level, is suggested by chart 4 and table 4. Thus after three months of adequate therapy, the two groups having reached much the same average hemoglobin level, that group whose medication was cut exhibited a moderate decrease in hemoglobin during the ensuing three months, whereas the group whose medication was maintained showed a slight gain. On applying statistical methods of computation and using the formula $\sigma = \pm \sqrt{\frac{\Sigma a}{n-1}}$, in which a represents the deviation from the mean and n the number of observations, it was found that these differences in hemoglobin level at the end of six months' study are not great enough to be considered statistically significant. Nevertheless, the two divergent trends suggest that supplemental iron is of advantage in maintaining an optimal hemoglobin level in infants up to the age of 2 years. Possibly a smaller dose of ferrous sulfate than 6 grains daily would suffice to maintain the hemoglobin level in the neighborhood of 14 Gm., once it is raised to that point.

SUMMARY

A study was made of 64 normal white American-born boys and girls ranging from 3 months to 2 years in age and living under the same conditions in an institution having good pediatric supervision.

There being no other known variable, half of the infants were each given 30 grains of iron and ammonium citrates (about 340 mg. of metallic iron) daily; the control infants were each given 6 grains of ferrous sulfate (about 78 mg. of metallic iron) daily. Therapy was continued for three months, the effects being checked by estimations of red cell count, hemoglobin and red cell volume.

As indicated by increases in hemoglobin (chart 3), the ferrous iron proved to be as effective as the ferric. Chart 3 suggests that 14 Gm. of hemoglobin per hundred cubic centimeters of blood is the optimal level to be expected from administration of these forms and doses of iron, continued for three months, for infants of this age period.

The two groups having reached much the same average hemoglobin level at the end of three months, one group was then withdrawn from iron therapy while the other group continued to receive supplemental iron for an additional three months. The trend of the hemoglobin level was downward in those infants whose medication was discontinued, whereas it was upward in those for whom medication was maintained (chart 4).

It seems probable that the increases in hemoglobin were the result of generous supplements of iron alone rather than of the traces of copper which contaminated both iron compounds.

This study confirms the claim that seemingly normal babies between the ages of 3 months and 2 years have a borderline anemia and demonstrates that their hemoglobin levels can be raised to about 14 Gm. per hundred cubic centimeters by treatment with adequate iron without added copper. Increases in the number and volume of red cells also result, though they are less marked. Improvements in the infants' color, activity and resistance to infection are believed to result, though they are difficult to measure. In this investigation ferrous iron produced a maximum effect with much smaller doses than ferric, and it caused no gastrointestinal disturbance. Some supplemental iron appears to be needed, up to the age of 2 years at least, to maintain the hemoglobin at this optimal level; it is possible that less than 6 grains of ferrous sulfate would be an adequate maintenance dose.

Helpful suggestions were given throughout this investigation by Prof. John C. Gittings, Dr. Joseph Stokes Jr., Dr. Milton Rapoport and Dr. Arthur D. Waltz.

ADDITION OF VEGETABLE SOUP AND STRAINED VEGETABLES TO DIET OF ARTIFICIALLY FED INFANTS

M. W. POOLE, M.D.

B. M. HAMIL, M.D.

T. B. COOLEY, M.D.
AND
I. G. MACY, PH.D.
DETROIT

Although modern pediatric practice emphasizes the early use of vegetables in the diet of the young child, there is a need for more definite scientific information on the age at which they can be introduced into the diet most advantageously, the form in which they should be given, the mode in which they are utilized and their actual influence on metabolism. In recent years there has been an urge to develop children up to or beyond a theoretical average or an erroneously called normal weight for age and height. Whether the bigger and more rapidly growing baby is the ideal is a question deserving the most intense scientific study. The goal to be striven for includes physical perfection and the greatest possible mental development for every child through adequate dietary measures and proper hygiene.

Vegetables added to the diet of infants have been taken as a matter of course, but medical opinion has been widely divided as to the right time for the addition. Pediatric textbooks published as late as 1911 advised that carrots, stewed tomatoes and other vegetables sometimes used be given with extreme caution to children of 3 to 6 years. Griffith [1] recommended the avoidance of cabbage, cauliflower, raw celery and raw tomatoes—items which are now commonly included in the child's diet. Morse [2] in 1926 recommended the addition of some vegetables to the diet

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From the Research Laboratory of the Children's Fund of Michigan in cooperation with the Children's Hospital of Michigan.

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1. Griffith, J. P. C.: The Care of the Baby, Philadelphia, W. B. Saunders Company, 1911.

2. Morse, J. L.: Clinical Pediatrics, Philadelphia, W. B. Saunders Company, 1926, p. 189.

at the age of 1½ to 2 years, while Hess [3] and Brennemann [4] stated that from 5 to 8 months is the proper age for introducing vegetable soup into the diet. Brennemann said: "My own tendency for years has been to slide the whole sequence of additional foods farther and farther down the scale of months, always only because babies seemed to do better if I began still earlier than I had done." In discussing his own routine of infant feeding at the sixth month he stated that "if the vegetables are finely divided by being sieved, or adequately mashed, they rarely give rise to any trouble at this age." At the extreme end of the scale, Caldwell [5] reported observations on a series of 60 infants who were fed strained vegetables between the ages of 6 weeks and 9 months and found that with few exceptions every child in the series thrived and progressed in a manner which gave evidence that this form of feeding contributed in a large measure to its physical development and well-being.

The scientific data on the kinds of vegetables best suited for specific nutritive purposes and on the tolerance, digestibility and utilization of vegetables by the human infant are too few and too conflicting to warrant definite conclusions. Realizing that there must be no shortage in any of the dietary essentials when they are building toward nutritional stability and an optimal plane of health, pediatricians and nutritionists have been increasing the variety of the vegetables as well as adding them earlier and earlier. The advantages usually accredited to vegetables in the diet of infants are increased gastrointestinal motility, improved appetite, the addition of vitamins and the increased intake of minerals, particularly iron, calcium and phosphorus, and the psychologic effects of acquiring desirable dietary habits. Fat and other ether-soluble nutrient materials, carbohydrate, fiber and perhaps hitherto unrecognized substances are also introduced into the diet by vegetables.

MEDICAL AND DIETARY PROBLEMS INVOLVED IN VEGETABLE FEEDING OF INFANTS

Alimentary (nutritional) anemia, which develops when the young growing organism is deprived of adequate iron in its food, was described by Czerny.[6] The researches of Bunge [7] on animals and those of

3. Hess, J. H.: Feeding and Nutritional Disorders in Infancy and Childhood, Philadelphia, F. A. Davis Company, 1927, p. 148.

4. Brennemann, J., in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 2, chap. 23, p. 705.

5. Caldwell, G. W.: The Nutritive Value of Strained Vegetables in Infant Feeding, J. Pediat. **1**:749, 1932.

6. Czerny, A., and Keller, A.: Des Kindes Ernährung und Ernährungs-Störunges, ed. 2, Leipzig, Franz Deuticke, 1928.

(Footnotes continued on next page)

Hugounenq [8] on the human infant have shown that in the young of several mammals there was at birth a large supply of stored iron, which diminished progressively until mixed food was taken. This anemia may develop either in the full term or the premature infant, but the latter is more susceptible because his more rapid growth makes greater demands on the antenatal stock of iron. This deficiency in formation of blood may be due to an inadequate supply of available hematogenic materials other than iron and possibly also to hypoplasia of the marrow or to increased destruction of blood.[9] The antianemic value of inorganic iron in combination with copper [10] was demonstrated first by the effectiveness of vegetables and fruits or of their ashes in stimulating regeneration of hemoglobin in rats with anemia produced by a milk diet.[11] However, not all the iron contained in vegetables is available for utilization, as some of it is bound in organic compounds, particularly hematin.[12] Shackleton and McCance [13] studied the ionizable iron in 153 common British foods and came to the conclusion that "the percentage

7. Bunge, G.: Ueber die Aufnahme des Eisens in dem Organismus des Säuglings, Ztschr. f. physiol. Chem. **13**:399, 1889; Weitere Untersuchungen über die Aufnahme des Eisens in dem Organismus des Säuglings, ibid. **16**:173, 1892; Ueber die Aufnahme des Eisens in dem Organismus des Säuglings (Nachtrag), ibid. **17**:63, 1892.

8. Hugounenq, M. L.: Recherches sur la statique des éléments minéraux et particuliérement du fer chez le foetus humain, Compt. rend. Soc. de biol. **51**:337, 1889.

9. The Anemia of Premature Infants, editorial, J. A. M. A. **104**:565 (Feb. 16) 1935.

10. Hart, E. B.; Steenbock, H.; Elvehjem, C. A., and Waddell, J.: Iron in Nutrition: I. Nutritional Anemia on Whole Milk Diets and the Utilization of Inorganic Iron in Hemoglobin Building, J. Biol. Chem. **65**:67, 1925. Waddell, J.; Elvehjem, C. A.; Steenbock, H., and Hart, E. B.: Iron in Nutrition: VI. Iron Salts and Iron-Containing Ash Extracts in the Correction of Anemia, ibid. **77**:777, 1928. Hart, E. B.; Steenbock, H.; Waddell, J., and Elvehjem, C. A.: Iron in Nutrition: VII. Copper as a Supplement to Iron for Hemoglobin Building in the Rat, ibid. **77**:797, 1928. Mitchell, H. S., and Miller, L.: Studies in Nutritional Anemia: Quantitative Variations in Iron, Copper and Manganese Supplements, ibid. **92**:421, 1931.

11. Mitchell, H. S., and Miller, L.: Inorganic Elements of Spinach in the Treatment of Nutritional Anemia, J. Biol. Chem. **85**:355, 1929-1930. Sheets, O.; Frazier, E., and Sulzby, A.: The Effect of Feeding Green Leafy Vegetables on Nutritional Anemia as Compared with Feeding Liver, in Forty-Third Annual Report, Mississippi State Report, 1930, p. 23. Levine, H.; Culp, F. B., and Anderson, C. B.: The Value of Some Vegetables in Nutritional Anemia, J. Nutrition **5**:295, 1932.

12. Elvehjem, C. A.: The Relative Value of Inorganic and Organic Iron in Hemoglobin Formation, J. A. M. A. **98**:1047 (March 26) 1932.

13. Shackleton, L., and McCance, R. A.: The Ionisable Iron in Foods, Biochem. J. **30**:582, 1936.

of the total iron in ionizable form may be a more characteristic feature of any particular material than the total amount of iron in it."

Adults [14] are apparently able to utilize the calcium of vegetables satisfactorily, as shown by the metabolic balance method of study, but children [15] and infants [16] have shown contradictory and unconvincing results. The decreased utilization of the calcium in such vegetables as carrots and spinach has been attributed to the high bulk of these vegetables.[17] Other factors have been under investigation since it was shown in 1935 that spinach, in contrast to other green leafy foods, contains enough oxalic acid to inhibit utilization of calcium.[18] In the process of digestion the affinity of free oxalic acid for calcium must be satisfied. This means that calcium from sources other than spinach is utilized in formation of the insoluble calcium oxalate.

It has long been recognized that a large portion of the total phosphorus of foodstuffs may be present in the form of phytin (inositol-hexaphosphoric acid), which is probably not entirely available to the body, as it is not hydrolyzed by the intestinal enzymes.[19] It is important to note that green leaf and stem vegetables contain no phytin, while in

14. Blatherwick, N. R., and Long, M. L.: The Utilization of Calcium and Phosphorus of Vegetables by Man, J. Biol. Chem. **52**:125, 1922. McLaughlin, L.: Utilization of the Calcium of Spinach, ibid. **74**:455, 1927. Rose, M. S.: Experiments on the Utilization of the Calcium of Carrots by Man, ibid. **41**:349, 1920. Rose, M. S., and MacLeod, G.: Experiments on the Utilization of the Calcium of Almonds by Man, ibid. **57**:305, 1923.

15. Sherman, H. C., and Hawley, E.: Calcium and Phosphorus Metabolism in Childhood, J. Biol. Chem. **53**:375, 1922. Bonner, P.; Hummel, F. C.; Bates, M. F.; Horton, J.; Hunscher, H. A.; Poole, M. W., and Macy, I. G.: The Influence of a Daily Serving of Spinach or Its Equivalent in Oxalic Acid upon the Mineral Utilization of Children, J. Pediat. **12**:188, 1938.

16. Edelstein, E.: Der Einfluss von Gemüsezulagen auf den Stickstoff- und Mineralstoff-wechsel des Kindes, Ztschr. f. Kinderh. **52**:483, 1932; Nutrition Abstr. & Rev. **2**:130, 1932-1933. Schultz, F. W.; Morse, M., and Oldham, H.: Vegetable Feeding in the Young Infant: Influence on Gastro-Intestinal Motility and Mineral Retention, Am. J. Dis. Child. **46**:757 (Oct.) 1933.

17. Ascham, L.: The Influence of Bulk in the Diet upon Fecal Calcium and Phosphorus, J. Nutrition **3**:411, 1930. Bloom, M. A.: The Effect of Crude Fiber on Calcium and Phosphorus Retention, J. Biol. Chem. **89**:221, 1930. Burton, H. B.: The Influence of Cereals upon the Retention of Calcium and Phosphorus in Children and Adults, ibid. **85**:405, 1930. Whitacre, J.; Willard, A., and Blunt, K.: Influence of Fiber on Nitrogen Balance and on Fat in the Feces of Human Subjects, J. Nutrition **2**:187, 1929.

18. Kohman, E. F., and Sanborn, N. H.: Calcium Availability in Foods Containing Oxalates: A Preliminary Report, Indust. & Engin. Chem. **27**:732, 1935. Fincke, M. L., and Sherman, H. C.: The Availability of Calcium from Some Typical Foods, J. Biol. Chem. **110**:421, 1935.

19. Plimmer, R. H. A.: The Metabolism of Organic Phosphorus Compounds: Their Hydrolysis by the Action of Enzymes, Biochem. J. **7**:43, 1913.

fresh legumes (raw or cooked) only 5 to 20 per cent of the total phosphorus is in the form of phytin, according to the figures published by McCance and Widdowson.[20]

Vegetables and fruits contain many of the complex carbohydrates, some of which can be hydrolyzed in the body to a greater or lesser degree. From a recent investigation it is evident that hemicelluloses and pectins have a nutritive value that is clearly not caloric,[21] so that foods containing abundant amounts of these substances take on a role of greater importance. Small amounts of pectin have been shown to have a definite protein-sparing action, to have marked stimulative properties and to cause increased intestinal motility.

Increased rate of gastrointestinal action as a result of vegetable in the food is usually explained as follows: The increased bulk resulting from the indigestibility of the cellulose and of the cell membrane mechanically stimulates the intestine to contract. Rubner many years ago and other investigators more recently [21] have demonstrated that the laxative effect of vegetables is dependent not only on the crude fiber in the food but on the amount of gastrointestinal secretion called forth while the food is in the gastrointestinal tract.

It is probable that less than 50 per cent of the ether extract of green leaf food can be considered as a potential source of energy or food for the human being, because only the fatty acids or their compounds (glycerides, phospholipids) are readily digested and assimilated by man.[22] The ether extract is a mixture which contains not only true fats (glycerides of fatty acids) but sterols, waxes, phospholipids and pigments such as chlorophyll, xanthophyll and carotene. Only 27 to 41 per cent of this ether extract of cabbage and spinach leaf is in the form of fatty acids.[23]

It is therefore evident that a question remains as to what particular foods serve most advantageously for specific purposes and as to how much of the mineral content of the plant is readily available for metabolism.

The use of supplementary foods is important, however, for reasons beyond the actual physical need of the baby. Probably the most

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20. McCance, R. A., and Widdowson, E. M.: Phytin in Human Nutrition, Biochem. J. **29**:2694, 1935.

21. Manville, J. O.; Bradway, E. M., and McMinis, A. S.: Pectin as a Detoxication Mechanism, Am. J. Digest. Dis. & Nutrition **3**:570, 1936.

22. Horwitt, M. K.; Cowgill, G. R., and Mendel, L. B.: The Availability of the Carbohydrate and Fats of the Green Leaf Together with Some Observations on Crude Fiber, J. Nutrition **12**:255, 1936.

23. Horwitt, Cowgill and Mendel.[22] Chibnall, A. C., and Channon, H. G.: The Ether-Soluble Substances of Cabbage Leaf Cytoplasm, Biochem. J. **23**:176, 1929.

important additional consideration is the establishment of satisfactory eating habits. This is well summed up in the words of Aldrich [24]: ". . . almost all babies resent changes, whether they be changes of food, attendant, or clothing. If we are going to develop in a baby a pleasant concept of food, it is important that changes in the character of his food do not give rise to unpleasant struggles." In regard to vegetables, he says: "This is a much more radical change as the difference in taste is much greater than any he has experienced before. One vegetable should be given over a long enough period (usually one to two weeks) to accustom him to its taste before the baby is assaulted by another change. Each new vegetable should be tried in the same way."

PROBLEMS ARISING IN THE PREPARATION OF VEGETABLES FOR INFANTS

The commercial preparation of vegetable purée or of vegetable soup offers an advantage over the usual methods of home cooking, partly because the foods can be prepared in much larger quantities, which minimizes the variations found in analyses of the same species of raw vegetables.[25] Moreover, when the relatively small amounts of vegetable needed for a day's feeding are prepared, the same part of the vegetable may not always be used. The outer leaves of plants are usually richer in all minerals and vitamins,[26] which may account for a twentyfold difference in the calcium content of the prepared portions.

The change which home cooking produces in concentration of the available minerals and vitamins is an important dietetic consideration, as an infant ingests a relatively small amount of vegetable. Losses of inorganic salts in steam cooking may be as high as 30 per cent.[27] This

24. Aldrich, C. A.: Cultivating the Child's Appetite, New York, The Macmillan Company, 1928.

25. (*a*) Bishop, E. R.: The Calcium and Phosphorus Content of Some Alabama Vegetables, J. Nutrition **8**:239, 1934. (*b*) Tosconi, V., and Reznikoff, P.: The Iron Content of Foods Used in a Municipal Hospital, ibid. **7**:79, 1934. (*c*) Davidson, J., and LeClerc, J. A.: The Variation in the Mineral Content of Vegetables, ibid. **11**:55, 1936.

26. (*a*) Bishop and others.[25] (*b*) McCance, R. A.; Widdowson, E. M., and Shackleton, L. R. B.: The Nutritive Value of Fruits, Vegetables and Nuts, Medical Research Council, Special Report Series, no. 213, London, His Majesty's Stationery Office, 1936.

27. Courtney, A. M.; Fales, H. L., and Bartlett, F. H.: Some Analyses of Vegetables Showing the Effect of the Method of Cooking, Am. J. Dis. Child. **14**:34 (July) 1917. Peterson, W. H., and Hoppert, C. A.: The Loss of Minerals and Other Constituents from Vegetables by Various Methods of Cooking, J. Home Economics **17**:265, 1925. Culp, F. B., and Copenhaver, J. E.: The Loss of Iron,

(*Footnote continued on next page*)

may be due to the greater degree of shrinkage at higher temperatures, which causes expression of the fluids of the plant, or to the leaching effect of the condensed water dripping on the vegetable while it is being cooked.

Boiling usually makes little change in the weight of vegetables, but the leaching action of the surrounding water produces rapid and extensive loss of minerals and of nitrogen.[26b] This loss may amount to from 15 to 50 per cent of the minerals of the raw vegetables, depending on the kind of vegetable, the amount of water and the duration of cooking. Most of this water is ordinarily drained off. Such loss of water is prevented by commercial canning or even by home canning.

As properly prepared vegetables enhance the vitamin content of the infant's diet to an appreciable degree, it is essential to understand clearly the effects of cooking on these elements and to know how extensively they are found in the various vegetables and in which part of the plant they are most abundant.

Vitamin A is found in greatest concentration in the green and yellow portions of plants, carrots having the richest supply; the outer green leaves of lettuce, cabbage and spinach may be as much as thirty times richer in this substance than the bleached inner portions.[28] Tomatoes and peas have been found to have about three times the vitamin B (B_1) content of carrots or beans and five to eight times that of beets and spinach. Green leafy vegetables contain vitamin B_2 in appreciable concentration, while other vegetables are significantly poor in this substance. Uncooked tuber juices, carrots, turnips and tomatoes have a high vitamin C potency, and the leaves of cabbage, spinach, lettuce and endive have a low one. Vitamin A in general is fairly stable to heat with the ordinary method of cooking; for example, heating of filtered tomato juice at 97 C. for four hours [29] under aerobic or anaerobic conditions produced a 17 per cent loss of its vitamin A potency.

Destruction of vitamin B (B_1) by heat was found by Sherman and Burton [30] not to be entirely due to oxidation, as there was practically the same loss in tomato juice under aerobic and under anaerobic conditions.

Copper and Manganese from Vegetables Cooked by Different Methods, ibid. **27**:308, 1935. Flanley, M. G., and Johnson, E. M.: Iron Loss in Cooking Broccoli, ibid. **24**:821, 1932.

28. Sherman, H. C., and Smith, S. L.: The Vitamins, New York, The Chemical Catalog Company, Inc., 1931.

29. Sherman, H. C.; Quinn, E. J.; Day, P. L., and Miller, E. H.: The Relative Stability of Vitamin A from Plant Sources, J. Biol. Chem. **78**:293, 1928.

30. Sherman, H. C., and Burton, G. W.: Effect of Hydrogen-Ion Concentration upon the Rate of Destruction upon Vitamin B, J. Biol. Chem. **70**:639, 1926.

Hoff [31] found a decrease of vitamin B_1 in spinach after ordinary household cooking but no loss of vitamin B_2.

Vitamin C is notably the most easily destroyed of all by exposure to air, heat, or alkali.[28] The acid reaction of tomatoes protects the vitamin C in cooking, so that they retain their value in home use more than other vegetables. Fenton, Tressler and King,[32] using the newer chemical method for measuring vitamin C, showed that about one-half the vitamin C of fresh peas passes into the cooking water, the greater part of it in the first two minutes. This confirms the frequent observation that ordinary cooking, even for short periods, may destroy 50 per cent of the vitamin C in fruit and in vegetables.[33] The vitamin D content of vegetables is little influenced by ordinary methods of cooking or canning because of its relative thermostability.

In commercial canning many of the objectionable results of steaming or boiling vegetables by home methods can be overcome by particularly designed equipment. In addition, vegetables can be harvested and processed in large quantities, which makes for uniformity and the highest nutritive value of the product.

Eddy, Kohman and their co-workers [34] compared raw, cooked and commercially canned spinach, some of which had been stored for three years. They found that a given amount of raw spinach and its equivalent in canned form caused similar rates of growth in rats; this result showed that the canned spinach retained its original vitamin A potency. The same workers,[35] comparing the vitamin A in raw, cooked and canned peas, found that the canned products were slightly lower in vitamin A

31. Hoff, J. J.: Vergleichende Untersuchungen über den Einfluss des haushaltsüblichen Kochens und des Konservierens in Blechdosen auf den Vitamingehalt der Gemüse, Ztschr. f. Ernährung **3**:355, 1933; Nutrition Abstr. & Rev. **3**:1003, 1934.

32. Fenton, F.; Tressler, D. K., and King, C. G.: Losses of Vitamin C During the Cooking of Peas, J. Nutrition **12**:285, 1936.

33. (*a*) Langley, D. D.; Richardson, J. E., and Andes, E. J.: The Effect of Storage and Canning upon the Vitamin Content of Carrots, Bulletin 276, Montana State College, Agricultural Experiment Station, 1933. (*b*) Bukin, V. N.; Izmailova, N. A., and Bogochunaz, A. P.: Influence of Cooking of Vegetables on the Preservation of Vitamin C, Bull. Appl. Botany, Genetics and Plant Breeding, 1934, supp. 67, p. 129; Nutrition Abstr. & Rev. **4**:520, 1935. (*c*) Eddy, W. H., and Kohman, E. F.: Vitamin C in Canned Foods, Indust. & Engin. Chem. **16**:52, 1924.

34. Eddy, W. H.; Kohman, E. F., and Carlsson, V.: Vitamins in Canned Foods: III. Canned Spinach, Indust. & Engin. Chem. **17**:69, 1925. Eddy, W. H.; Kohman, E. F., and Halliday, N.: Vitamins in Canned Foods: VII. Effect of Storage on Vitamin Value of Canned Spinach, ibid. **21**:347, 1929.

35. Eddy, W. H.; Kohman, E. F., and Carlsson, V.: Vitamins in Canned Foods: IV. Green Peas, Indust. & Engin. Chem. **18**:85, 1926.

value. The mixed vegetable soup used in our investigation was found to be an excellent source of vitamin A, since 150 mg. contained more than 1 Sherman unit of this vitamin.[36]

In this study the strained peas, carrots and vegetable soup contained the following amounts of vitamins B_1 and B_2 (G) per ounce (453 Gm.):[37]

Vegetables	B_1 units	B_2 units
Peas	7–8	7.5–8.5
Carrots	4.3	2.5
Vegetable soup	3.0	3.0

For supplementary use in infant feeding, commercially canned strained vegetables appeared to have the greatest potency of vitamin C possible in vegetables cooked by any method appropriate for the young infant. It has been shown that by reducing the exposure to heat in the presence of oxygen factory methods retain a much higher content of vitamin C in vegetables and in tomato juice than can be secured by open kettle methods.[38]

Canning by modern methods not only prevents loss of minerals more efficiently than home cooking, but it preserves larger amounts both of the total iron and of the ionizable iron.[39] High temperatures and long contact with the liquid medium in commercial canning increase the availability and promote the better utilization of the minerals contained in the vegetables.[40]

PURPOSE OF STUDY AND METHODS OF PROCEDURE

The purpose of this investigation was to determine whether vegetable soup reenforced with wheat germ added to the diet of 228 infants[41]

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36. Hanning, F.: Canned Strained Vegetables as Sources of Vitamin A, J. Am. Dietet. A. **9**:295, 1933.

37. Hanning, F.: A Comparison of Vitamin B and G in Canned Strained Foods, J. Nutrition **8**:449, 1934.

38. (*a*) Eddy and Kohman.[33e] (*b*) Hanning, F.: Comparison of the Biological and Chemical Methods for the Determination of Vitamin C in Canned Strained Vegetables and a Study of Its Variation from Year to Year, J. Nutrition **12**:405, 1936. (*c*) Kohman, E. F.; Eddy, W. H., and Gurin, C. Z.: Vitamins in Canned Foods: XIII. Canning Tomato Juice Without Vitamin C Loss, Indust. & Engin. Chem. **25**:682, 1933.

39. Shackleton and McCance.[13] Tosconi and Reznikoff.[25b] Hanning.[38b]

40. Kohman, E. F.; Sanborn, N. H.; Eddy, W. H., and Gurin, C. Z.: Vitamins in Canned Foods: XIV. Calcium and Vitamin D in Foods, Indust. & Engin. Chem. **26**:758, 1934.

41. The infants were obtained through the cooperation of the Detroit Department of Health, Harper Hospital, Florence Crittenton Hospital, Woman's Hospital and private physicians in Detroit.

soon after birth (from the ages of 2 to 8 weeks) supplies a nutritive advantage, thereby contributing to nutritional stability and to a more desirable plane of health. In addition, strained vegetables were introduced during the fifth and sixth months and were continued throughout the entire first year of life. Criteria for the estimation of nutritional advantage, should any exist, were looked for in a series of anthropometric measurements, estimations of hemoglobin, red blood cell counts and roentgenograms of the long bones, as well as in the changes in weight and height which are usually accepted indexes of a good nutritional state. These babies lived in their own homes under the care of their own parents, with adequate nursing supervision. The technic of clinical procedure, measurements, roentgen photography and blood counts was described in previous papers.[42]

During the period of observation 2,197 visits to the clinic were made by these infants. Over 2,000 roentgenograms were made to check the appearance of the bones of the left extremities. On these particular groups of infants 33,228 anthropometric measurements were done at their monthly visits. The roentgenograms and measurements do not include those of babies who made only 1 or 2 visits before they were dropped from the study for various reasons.[43]

The basic diet of evaporated milk, water, and corn syrup with its supplements of powdered lemon juice[44] and cod liver oil[45] was

42. (*a*) Poole, M. W.; Hamil, B. M.; Cooley, T. B., and Macy, I. G.: The Stabilizing Effect of Increased Vitamin B (B_1) Intake on the Growth and Nutrition of Infants, Am. J. Dis. Child. **54**:726 (Oct.) 1937. (*b*) Colby, M. G.; Macy, I. G.; Poole, M. W.; Hamil, B. M., and Cooley, T. B.: Relation of Increased Vitamin B (B_1) Intake to Mental and Physical Growth of Infants, ibid. **54**:750 (Oct.) 1937. (*c*) Cooley, T. B., and Reynolds, L.: The Interpretation of X-Ray Films in Diagnosis of Rickets, J. Pediat. **10**:743, 1937. (*d*) Hamil, B. M.; Reynolds, L.; Poole, M. W., and Macy, I. G.: Minimal Vitamin C Requirements of Artificially Fed Infants: A Study of Four Hundred and Twenty-Seven Children Under a Controlled Dietary Regimen, Am. J. Dis. Child., to be published.

43. Martha Eliot, M.D., assistant chief, Children's Bureau, United States Department of Labor; Donald J. Barnes, M.D., and Florence Browne, M.D., of Detroit, cooperated in the study of the infants in groups I and I-v. E. M. Nelson, Ph.D., of the United States Department of Chemistry and Soils, furnished the standardized cod liver oil in measured quantities for daily use.

44. The dehydrated powdered lemon juice titrated 0.803 to 0.879 mg. of vitamin C per gram and contained 13 Sherman-Chase units of vitamin B_1 per gram.[42d]

45. One batch of standardized cod liver oil especially preserved and held in cold storage was used throughout the study for all groups except groups I and I-v, which received standardized cod liver oil furnished by the United States Children's Bureau and given in daily quantities of 250 and 300 U. S. P. units of vitamin D, respectively.

previously described in detail.[42a] The additions of vegetable soup[46] and strained vegetables are shown in table 1. One teaspoonful (5 Gm.) of strained vegetable soup was added to the twenty-four hour formula for the first two to four days, and this amount was then gradually increased until one-half can (8 teaspoonfuls [40 Gm.]) was being included in the daily feeding when the child was 6 to 8 weeks of age.

Groups I, I-v and I-pt received vegetables strained at home at the sixth month, while groups II and II-v were given commercially prepared peas and carrots from the fifth month of age to the end of the period of observation. In addition, all the babies were given strained fruit at the age of 6 or 7 months.

TABLE 1.—*Supplements of Vegetables to Basic Formula*

1934-1935	Number of Infants	Given from Beginning	Given Later
Group I[43] (control).....	51	None	Home cooked vegetable purée and potato at 6 mo. (⅔ tbsp. daily)
Group I-v[43]..... (vegetable soup)	60	½ can (32 cc.) vegetable soup daily	Same at 6 mo.
Group I-pt..... (premature twin)	13	½ can vegetable soup daily	Same at 6 mo.
1935-1936			
Group II (control).....	26	None	½ can commercially strained vegetable daily at 5 mo.; potato at 6 mo.
Group II-v..... (vegetable soup)	78	½ can vegetable soup daily	Same at 5 mo.; potato at 6 mo.

46. The strained vegetable soup was composed of peas, carrots, spinach, rice, barley, beef, tomatoes and celery (in order of decreasing occurrence) and wheat germ. The following chemical analyses of the vegetable soup, peas and carrots used in this study were furnished by the Gerber Products Company:

Percentage of Chemical Constituents of the Canned Strained Vegetables

	Carrots	Peas	Vegetable Soup
Total solids	8.92	14.47	10.90
Ash	0.45	0.47	0.25
Protein (N x 6.25).....	0.81	4.26	1.85
Fats (ether extract).....	0.04	0.35	0.05
Crude fiber	0.56	0.40	0.19
Carbohydrate other than fiber (by difference)	7.06	8.99	8.56
Calories per ounce.....	9	16	12
Calcium (as Ca O).....	0.0336	0.0230	0.0146
Phosphorus (as P_2O_5).....	0.0320	0.1399	0.0520
Iron (as Fe).....	0.0010	0.0020	0.0009

RESULTS AND COMMENT

As previously pointed out, the infants in the control group who received diluted evaporated milk acidulated with powdered lemon juice and supplemented with cod liver oil developed satisfactorily, as shown by the fact that they grew as well as or better than the average children in the series of the United States Children's Bureau and in the superior group of Stuart. Satisfactory as this basal formula undoubtedly was, the addition of commercially strained vegetable soup, carrots and peas might conceivably change the rate of growth, the plane of health or the hemoglobin level and red cell count because they introduced into the diet greater quantities of minerals, vitamins and the other nutrient substances mentioned. In a preventive study such as this the effects of these additions are not likely to be spectacular, because the control or basal diet left little to be desired from the standpoint of routine infant feeding. However, it is only reasonable to assume that any changes caused by the early feeding of vegetables should be noted in repeated observations on body growth in some of its dimensions, on the blood picture, on the roentgen appearance of the bones or on the person's ability to resist disease. These changes should be all the more readily detected in the group averages because we began the use of the vegetable soup at an early age, in some instances as early as the second week of life.

The 215 infants, born at full term, 5 premature infants and 8 twins included in this study during their first year of life were selected at an average age of 6 weeks, after they had been completely weaned from the breast and were physiologically stable so far as clinical examination could determine. The differences in the dietary additions of these children is shown in table 1. During the first year there was a high percentage of Negro infants in group I, which was compensated for in 1935-1936 by the use of 26 white infants as control group II. Thus when these two groups were combined the percentage of Negro children was essentially the same as in groups I-v and II-v. Throughout all our studies on growth the racial groups have been kept in the same proportion for the sake of uniformity, as some of the infants were also used in observations on antirachitic substances.

In general, the average increase in weight of the 138 infants born at full term (groups I-v and II-v) who received the vegetable soup as a supplement to a diet containing all the known nutritive essentials was similar to that of 77 infants born at full term (groups I and II) who received the same basic formula without the adjuvant of soup. It will be noted that the increase in weight was superior in the later months to that of the series studied by the Children's Bureau and about equal to that of the superior group reported on by Stuart (chart 1).

The average increase in height of these infants, as shown by the curves representing the combined groups I and II and I-v and II-v, was identical, but after the age of 130 days their heights were superior to the average heights represented by the Children's Bureau and by Stuart (chart 1).

The vegetable soup added about 36 calories to the twenty-four hour formula and approximately 10 Sherman-Chase units of vitamin B_1, bringing the total vitamin B_1 content to about 237 Sherman-Chase units. There was little difference in the average increase in weight of this group as compared with that of 76 infants who received 100 additional Sherman-Chase units of vitamin B_1 in their daily diet. The same close

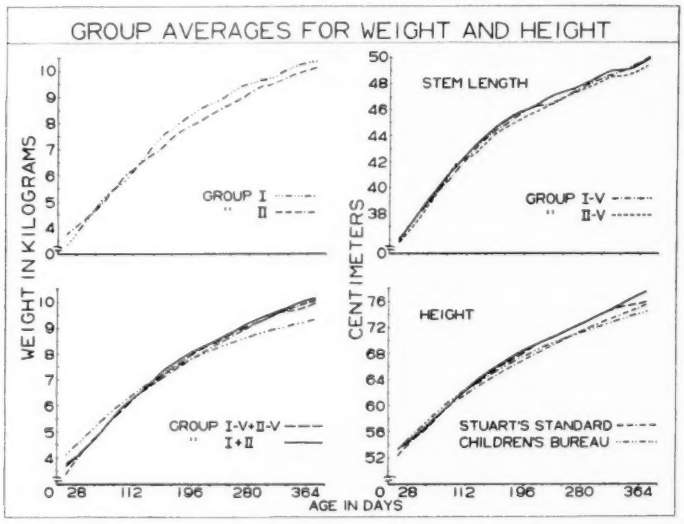

Chart 1.—This chart shows that the infants of this study grew as well as or better than average, as judged by a comparison of their average height and weight curves with those reported by Stuart and by the Children's Bureau. A dietary supplement of vegetable soup did not tend to increase average growth in stem length.

parallelism is also seen in the curves of average height of the same two groups of infants. In both average weight and average height there was a questionable superiority in favor of those who had the addition of vegetable soup in their diet.

Although the infants of groups I and II received the same dietary treatment up to the fifth month (at which time the latter were given the commercially prepared carrots and peas), there was a superiority in the averages of both height and weight for group II. This became evident in the weight curve from the one hundred and twenty-fifth day (chart 1). The difference may partly be due to the relatively high percentage of Negro infants in group I, as previously noted.

The average stem length (chart 1) was questionably superior for the combined groups I and II. It is evident, therefore, that the addition of the vegetable soup did not tend to increase stem length.

The average tibial length, which was measured by the small caliper, represented one of the component parts of total length and height. The curves for the control groups (I and II) and for experimental groups (I-v and II-v) are approximately the same (chart 2).

Measurements were made of the different parts of the tibia from roentgenograms taken on the infants' admission to the clinic and approximately at the sixth and at the ninth month. The average lengths

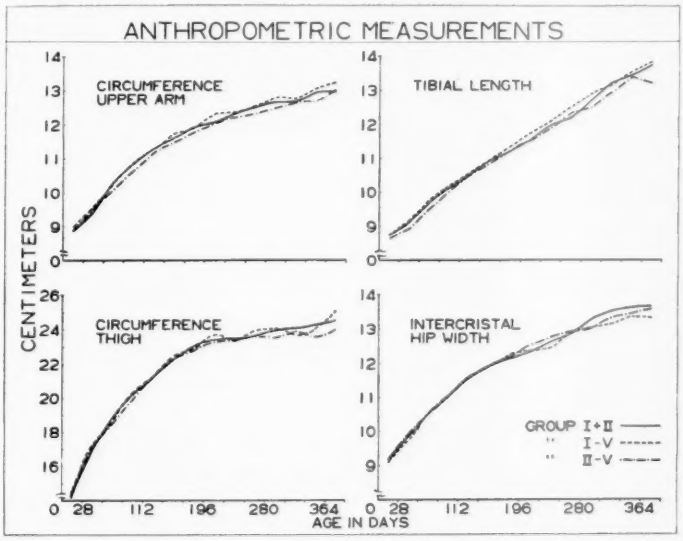

Chart 2.—This chart shows that growth as expressed by the average increase in the circumference of the upper arm and of the thigh, in tibial length and in intercristal hip width was unaffected by a dietary supplement of vegetable soup.

of the tibia in the control groups did not differ from those in the experimental groups. There was, however, an unexplainable advantage in favor of groups I and II in the diameter of the diaphysis of the left tibia. The average diameter of the distal metaphysis shows a questionable advantage in favor of groups I and II.

The combined control groups, which did not receive supplementary vegetable soup, compare favorably in average intercristal widths with groups I-v and II-v, who were given vegetable soup and, subsequently, commercially strained vegetables (chart 2). The measurements of biacromial width, which are less accurate, also reveal little difference between the special dietary groups and the combined control groups.

Included in the anthropometric measurements are three body circumferences, those of the thorax, the upper part of the arm and the thigh. As the measurements of the arm and the thigh are considerably influenced by the nutritional state of the body, it is reasonable to expect that any nutritive advantage of a dietary supplement might be reflected here. Chart 2 shows the averages for circumference of the arm and the thigh. Little difference is noted between the groups. This is also true of the average measurements of the chest.

The average number of erupted teeth at the various age levels was greatest in the combined control groups and lowest in group II-v. The mean age of eruption of the first tooth in the combined control groups I and II was 215 days; in group I-v, 226 days, and in group II-v, 216 days. It must be noted in this connection that these infants received each day 240 to 600 U.S.P. units of vitamin D in the form of standard-

TABLE 2.—*Occurrence of Infections, Diarrhea and Eczema*

	Group I	Group I-v	Group II	Group II-v
Number of babies	51	60	26	78
Visits to clinic	497	639	272	789
Clinic visits per baby	9.7	10.6	10.5	10.1
	Per Baby	Per Baby	Per Baby	Per Baby
Nasopharyngitis: mild	1.65	1.80	1.38	1.76
moderate and severe	0.25	0.62	0.73	0.49
Otitis media	0.16	0.08	0.31	0.13
Bronchitis and pneumonia	0.20	0.07	0.19	0.20
Diarrhea	0.27	0.37	0.15	0.24
Specific diseases	0.31	0.30	0.15	0.33
Eczema	0.24	0.18	0	0.26

ized cod liver oil, an amount considered by most recent investigators to be adequate for average infants during the first year.[47]

A decreased resistance to bacterial infection is recognized as one of the accompaniments of a diet poor in the various dietary essentials or accessories, but there is no uniformity of opinion as to whether increased resistance results from adding these items to a well balanced daily ration. After reviewing the literature concerning the relation of nutrition to infection, Clausen [48] stated:

"There is also no evidence that a good diet will decrease the number of infections during the first six months of life. There is some evidence that an adequate diet in the early months of life may decrease the severity of infection during the latter part of the first year and during the second."

47. Eliot, M. M.; Nelson, E. M.; Barnes, D. J.; Browne, F. A., and Jenss, R. M.: A Study of the Comparative Value of Cod Liver Oil, Viosterol and Vitamin D Milks in the Prevention of Rickets and of Certain Basic Factors Influencing Their Efficacy, J. Pediat. **9**:355, 1936.

48. Clausen, S. W.: Nutrition and Infection, J. A. M. A. **104**:793 (March 9) 1935.

From table 2 it is seen that there is little difference in amount of illness between the various groups when the figures of control groups I and II are combined. Eczema was infrequent, and the incidence was not always influenced by withdrawal of strained vegetables or vegetable soup. The food was well tolerated and well digested and was not a factor in the occurrence of the few cases of diarrhea. In most of these the condition was of the parenteral type and was associated with infection of the respiratory tract. There did not appear to be any difference in the number of cases of diarrhea whether the babies were fed vegetables strained at home or commercially prepared.

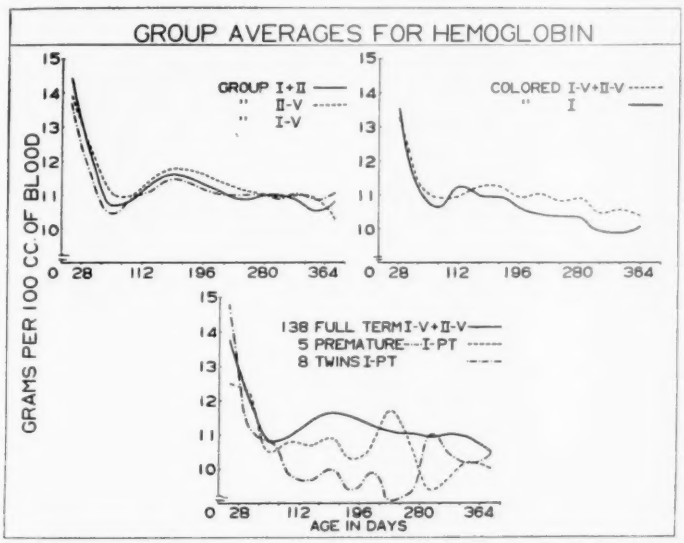

Chart 3.—This chart shows the racial tendency of the Negro infants to a lower average hemoglobin value and shows that they derived benefit from early feeding of vegetables. The early addition of vegetable soup and of strained vegetables did not prevent the onset of nutritional anemia in a small series of premature infants and twins.

During this study of 228 infants, which extended over a period of twenty-two months, 2,379 hemoglobin determinations and red cell counts were made. In this report we present only the hemoglobin values.

Because of the fact that vegetables have been shown to be a source of iron in a form readily available and capable of stimulating the production of hemoglobin in rats, observations on the human infant fed vegetables in the period of most rapid growth are particularly important. Comparison of the average hemoglobin levels of the infants who received strained vegetable soup as early as the second week of life (group I-v and II-v) with the levels of those who did not have this addition (groups I and II) shows that the physiologic fall of the hemoglobin level was least in group II-v and greatest in group I-v (chart 3). After this initial

fall the group averages rose to about the same level near the age of 100 days. Thereafter until approximately the age of 280 days those of group II-v maintained an appreciably higher average level. Beyond this age the averages of the combined control group fell below those of the other groups. The distinct superiority of the hemoglobin averages in group II-v was not entirely due to the addition of vegetable soup and vegetable purée to their diet, because the amount of vegetable soup used in the early months was the same as that given to the babies of group I-v during the previous year. The superior average hemoglobin levels of this series of babies may have been favorably influenced by the use of a larger amount of milk in their formulas at a younger age and by the earlier addition of cereals, strained vegetables and strained fruits (at the ages of 4, 5 and 6 months, respectively).

The Negro infants, who have a racial tendency to a lower average hemoglobin value, according to results of hematologic studies in this laboratory,[49] show benefit from early feeding of vegetables. The average hemoglobin values were higher for the Negro infants (Negro I-v and II-v) who received the vegetable soup than in those who did not (Negro I), as shown in chart 3.

Because anemia tends to develop during the early life of twins and of premature infants, it seemed desirable to observe a small number of such infants in this study in order to determine whether there was any justification for observing the effects of early feeding of vegetables on a larger group at some later time. Chart 3 shows the unsatisfactory response of 5 premature infants and 8 twins who were given the supplement of vegetable soup. One pair of twins required active medical treatment because of the grave nature of the anemia that developed.

SUMMARY

Supplementing the diet of 215 infants born at full term, 5 premature infants and 8 twins with commercially canned vegetable soup did not produce any digestive upsets or diarrhea that could be attributed to the vegetable feeding. The vegetable soup was incorporated in the formula from the time of the infant's first visit to the clinic. The transition to solid food was made easily by starting the feeding of cereals and vegetable purées at the fourth and at the fifth month.

Owing to the adequacy of the basal diet, which consisted of evaporated milk, water, corn syrup, powdered lemon juice and cod liver oil, the vegetable soup did not significantly influence the averages for growth in weight or the averages for growth in linear dimensions, such as total height, stem length and length of the tibia and of its various parts. The same is true for the biacromial and intercristal widths and

49. Munday, B.; Shepherd, M. L.; Emerson, L.; Hamil, B. M.; Poole, M. W., and Macy, I. G.: Hemoglobin Differences in White and Negro Infants, Am. J. Dis. Child. **55**:776 (April) 1938.

for the circumferences of the arm, thigh or chest, as judged by group averages.

There were no material differences in growth and dentition, as shown by group averages, whether home-prepared strained vegetables were added at the sixth month or commercially prepared strained carrots and peas were added at the fifth month, although it has been demonstrated that the canned purées have more available minerals. It is probable that on the basal formula the infants received their maximum impulse for growth, so that further increase of minerals or of vitamins in the vegetable soup or in the commercially strained vegetables added at the fifth month did not produce any further increment in the various body measurements or in total body weight.

There did not appear to be any significant difference in the rate of incidence of the various types of infection when the control groups were compared with those receiving the supplement of vegetable soup. The mortality rate during the two year period was one-fourth that reported by the State of Michigan for 1934 (52.14 per thousand live births).[50] Few cases of eczema were found in the entire study.

On these 288 infants 2,379 estimations of hemoglobin were made. Group averages showed a superiority of hemoglobin values in the infants who received canned vegetable soup during 1935-1936 but who also had a greater amount of milk in the formula at an earlier age, with the addition of cereal at 4 months, canned vegetable purée at 5 months and strained fruit at 6 months. The response of infants who were given vegetable soup during 1934-1935, with less milk in the early weeks and later supplements of cereals, purées and fruits, was not so satisfactory, as judged by the average hemoglobin level.

Average hemoglobin values for Negro infants who were getting early supplements of vegetable soup were higher than for the Negro infants who were not. The averages for both Negro groups, however, were lower than the averages for the composite groups.

The early addition of vegetable soup and of strained vegetables did not prevent the onset of nutritional anemia in a small series of premature infants and twins.

Dr. Lawrence Reynolds, roentgenologist, directed the taking and interpreting of the roentgenograms in the studies on infant growth and made many constructive suggestions in the conduct of this work.

Senia Kangas, R.N., director of the nursing service; Rachel Moore, roentgen technician; Betty Munday, M.A., Louise Emerson, B.A., and Marion Lange Shepherd, B.A., laboratory technicians, and Francis Slyker, Ph.B., statistician, assisted in this work.

50. Deacon, W. J. V.: The Influence of Respiratory Diseases on the Infant Mortality Rate, Michigan Pub. Health **24**:43, 1936.

INSENSIBLE PERSPIRATION IN CHILDREN

IV. THE INFLUENCE OF SALT

GEORGE J. GINANDES, M.D.
AND
ANNE TOPPER, M.D.
NEW YORK

Many investigators [1] have called attention to the close relation between the total heat production and the amount of heat dissipated through insensible perspiration. Soderstrom and DuBois [2] have shown that the proportion of dissipated heat is about 24 per cent in normal as well as in diseased subjects. Levine and his associates [3] demonstrated that about the same proportion exists in infancy. In a previous publication [4] we have shown that this relation holds throughout childhood. So constant is the correlation, in fact, that formulas have been derived and graphic curves have been constructed which enable one to make a reasonably accurate prediction of the total energy metabolism from the measured insensible loss of weight.[5] This correlation is maintained at any level of the body temperature, so long as that level remains constant.

It is important to note that the correlation between the total heat production and the amount of heat lost through insensible perspiration

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From the pediatric service of Dr. Béla Schick, Mount Sinai Hospital.

1. Benedict, F. G., and Root, H. F.: Insensible Perspiration: Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38**:1 (July) 1926. Johnston, M. W., and Newburgh, L. H.: J. Clin. Investigation **8**:147, 1930. Jores, A.: Ztschr. f. d. ges. exper. Med. **71**:170, 1930; **77**:734, 1931. Heller, H., and Schwartz, A.: ibid. **71**:416, 1930. Magendantz, H.: Deutsches Arch. f. klin. Med. **173**:44, 1932. Levine, S. Z., and Marples, E.: The Insensible Perspiration in Infancy and in Childhood: III. Basal Metabolism and Basal Insensible Perspiration of the Normal Infant; a Statistical Study of Reliability and of Correlation, Am. J. Dis. Child. **40**:269 (Aug.) 1930.

2. Soderstrom, G. F., and DuBois, E. F.: Clinical Calorimetry: XXV. The Water Elimination Through Skin and Respiratory Passages in Health and Disease, Arch. Int. Med. **19**:931 (May) 1917.

3. Levine, S. Z., and Wilson, J. R.: Respiratory Metabolism in Infancy and in Childhood: IV. Elimination of Water Through the Skin and Respiratory Passages, Am. J. Dis. Child. **33**:204 (Feb.) 1927.

4. Ginandes, G. J., and Topper, A.: Insensible Perspiration in Children: III. Statistical Correlation of Insensible Perspiration and Basal Metabolism, Am. J. Dis. Child. **53**:705 (March) 1937.

5. Peters, J. P.: Body Water, Springfield, Ill., Charles C. Thomas, Publisher, 1935, chap. 7, pp. 149-178.

is disturbed in conditions associated with disorders of body hydration.[6] Levine and Wyatt [7] observed a lowered rate of insensible loss in dehydrated infants with normal heat production. In the course of our experiments, we have likewise noted a lack of correlation between total heat production and insensible perspiration in children affected by known disturbance in body hydration.

Manchester, Husted and McQuarrie [8] studied the problem experimentally. These authors demonstrated that when they dehydrated their subjects by means of special diets and restriction of water, the insensible loss of weight was less than that predicted from the total heat production. On the other hand, in the excessively hydrated state the converse was true.

Gilman and Barbour,[9] in an attempt to analyze the basis of this dissociation, made a more fundamental study of the relation of body hydration to insensible perspiration and total heat production. These workers administered single doses of salt to rabbits and measured the osmotic pressure of the blood as well as the insensible perspiration of these animals. The osmotic pressure was taken as an index of the state of body hydration. These observers found that salt effected changes in the insensible perspiration, which varied inversely with the osmotic pressure of the blood. The total heat production remained unchanged. Although no quantitative relation could be established, these experiments explained on a physical basis the dissociation between heat production and heat loss through insensible perspiration in states of altered body hydration, confirming the conception that insensible perspiration is a function not only of heat regulation but of the state of body hydration.

A search of the literature for observations on the human subject of the type reported by Gilman and Barbour for their experimental rabbits revealed only scant reports.[10] The results of these reports are at variance with those of Gilman and Barbour. Believing that certain omissions and discrepancies in technic might account for this, we decided to restudy the problem.

PROCEDURE

The subjects used were hospital normal children varying in age from 6 to 10 years. Fifty-two experiments were made on nine such children, of which two were girls and seven boys. Their weights ranged from 17 to 32 Kg. The Sauter

6. Robert, F.: Arch. f. exper. Path. u. Pharmakol. **164**:367, 1932. Lavietes, P. H.: J. Clin. Investigation **14**:57, 1935.

7. Levine, S. Z., and Wyatt, T. C.: Insensible Perspiration in Infancy and in Childhood: IV. Basal Measurements in Dehydrated Infants, Am. J. Dis. Child. **44**:732 (Oct.) 1932.

8. Manchester, R. C.; Husted, C., and McQuarrie, I.: J. Nutrition **4**:39, 1933.

9. Gilman, A., and Barbour, H. G.: Am. J. Physiol. **104**:392, 1933.

10. Chrometzka, F., and Schweder, M.: Ztschr. f. d. ges. exper. Med. **80**:288, 1931. Hall, J. F., and McClure, G. S.: Am. J. Physiol. **115**:670, 1935.

balance was used to determine insensible loss of weight. The explanation of the term hospital normal, the procedure followed, and the balance itself have been fully described in previous publications.[11]

Single doses of salt were administered to these subjects, and their insensible perspiration and total heat production were then measured. Preliminary studies were made to determine the most suitable vehicles for administering the salt. This was necessary in order to avoid a stimulating effect of the vehicle itself and at the same time to minimize the disagreeable reaction resulting from the taste of salt. We found it best to administer the salt either in gelatin capsules or in tomato juice. When capsules were used, from 30 to 200 cc. of water was allowed. When the salt was given in tomato juice, up to 200 cc. of the menstruum was used. The dose of salt varied from 5 to 15 Gm.

Control experiments (table, experiments 4, 10, 11, 32, 36, 40, 42, 44, 46, 48 and 50) demonstrated that the vehicles in the quantities given exercised no influence on insensible perspiration. In one case (case 2, experiments 12 and 13) herring was used as the source of salt. In this case, an increase in insensible perspiration was noted which began about two hours after ingestion of the herring and lasted about two hours. The basal metabolism of this subject similarly showed an increase. The specific dynamic action of food, which influenced these experimental results, made this method of administering salt undesirable.

In several of our earlier experiments, the salt was given at about 9:30 a. m. Weighings began promptly after this, but no change in the rate of insensible loss of weight was observed until about 11 or 11:30 a. m. Observations made after this time prolonged the period of fasting and made the children restless and uncomfortable. The results therefore were discarded, and we decided to administer the salt at about 8 or 8:30 a. m. Weighings began about 9:30 and lasted until about 11:30 a. m. In this way we were able to observe when the action of the salt began, and when it started to wane, without unduly protracting the experiments. The basal insensible perspiration of every subject was studied for several days prior to administration of the salt. This provided adequate control for the days of testing with salt.

The relative amount of salt administered varied from 0.23 to 0.65 Gm. per kilogram of body weight. No attempt was made to ascertain whether any level exists below which the salt fails to show its effect, nor was any attempt made to find an upper level at which a maximum effect might be demonstrated. Our purpose was to administer the salt in such doses as to produce a physiologic effect without inducing discomfort.

The rate of the basal insensible perspiration in these experiments was calculated exactly, as in our previous work. As heretofore, a one hour period of adjustment was allowed. The same method was used on days when salt was given. A reaction due to salt was noted during the latter part of the period of adjustment. However, the maximum salt effect was noted from approximately two to three hours after administration of the salt, lasting throughout the hour immediately following the period of adjustment. We therefore retained this period and thus obviated certain discrepancies which otherwise might not be accounted for. The return to a normal rate of insensible loss of weight was gradual. The curve

11. Ginandes, G. J., and Topper, A.: Insensible Perspiration in Children: I. Experimental Procedure and the Influence of Certain Factors, Am. J. Dis. Child. **52**:528 (Sept.) 1936; II. Statistical Correlation of Insensible Perspiration and Various Body Measurements; Proposed Basal Standards for Children, ibid. **52**:1335 (Dec.) 1936.

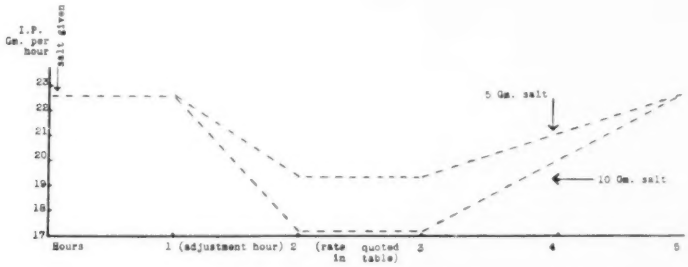
Subject	Experiment	Total Dose Salt, Gm.	Dose, Gm. per Kg.	Vehicle	Gm. I. P. per Hour	Percentage of Deviation from Average Basal I. P.	Basal Metabolism, Total Calories	Percentage of Deviation from Average B. M.
1. H. G., girl;	1	Control day		.....	23.95	.....	810	..
age, 6 yr.;	2	Control day		.....	21.23	.....	801	..
weight, 22 Kg.;	3	Control day		.....	22.64	.....	840	..
height, 115 cm.	4	0	....	35 cc. water	22.22	.....	843	+3
	5	5	0.23	Capsules, 35 cc. water	17.50	22.3 decrease	828	+1
	6	5	0.23	Capsules, 35 cc. water	16.82	25.3 decrease	...	..
	7	5	0.23	Capsules, 35 cc. water	17.20	23.6 decrease	843	3
2. R. H., boy;	8	Control day		.....	20.50	.....	912	..
age, 7 yr.;	9	Control day		.....	21.10	.....	890	..
weight, 18 Kg.;	10	0	....	75 cc. water	20.00	.....	...	..
height, 120 cm.	11	0	....	35 cc. tomato juice	21.00	.....	881	..
	12	..	....	30 Gm. pickled herring	23.80	15 increase	1,004	+13
	13	..	....	30 Gm. pickled herring	25.00	21 increase	1,028	+15
	14	5	0.28	35 cc. tomato juice	17.80	15 increase	907	+1
	15	5	0.28	35 cc. tomato juice	17.00	18 decrease	893	0
	16	5	0.28	Capsules, 50 cc. water	16.50	20 decrease	880	0
	17	5	0.28	Capsules, 50 cc. water	17.10	18 decrease	898	0
	18	10	0.56	Capsules, 75 cc. water	15.50	25 decrease	900	+1
	19	Control day		.....	22.20	.....	884	0
3. S. S., boy;	20	Control day		.....	22.64	.....	734	..
age, 6 yr.;	21	Control day		.....	23.00	.....	730	..
weight, 17 Kg.;	22	5	0.29	Capsules, 100 cc. water	19.20	16 decrease	712	−3
height, 107 cm.	23	10	0.58	Capsules, 150 cc. water	17.00	25 decrease	729	−1
4. H. S., boy;	24	Control day		.....	25.26	.....	1,080	..
age, 8 yr.;	25	Control day		.....	24.80	.....	1,123	..
weight, 28 Kg.;	26	10	0.35	75 cc. tomato juice	20.90	17 decrease	1,145	+4
height, 134 cm.	27	10	....	75 cc. tomato juice	20.50	18 decrease	1,097	0
5. H. R., girl;	28	Control day		.....	23.10	.....	1,152	..
age, 10 yr.;	29	Control day		.....	24.40	.....	.....	..
weight, 32 Kg.;	30	10	0.31	50 cc. tomato juice	17.90	25 decrease	.....	..
height, 138 cm.	31	15	0.47	75 cc. tomato juice	17.30	27 decrease	1,101	−5
	32	0	....	75 cc. tomato juice	22.64	.....	.....	..
6. H. S., boy;	33	Control day		.....	21.00	.....	874	..
age, 8 yr.;	34	Control day		.....	20.90	.....	...	..
weight, 23 Kg.;	35	10	0.43	Capsules, 100 cc. water	17.47	17 decrease	873	0
height, 124 cm.	36	0	....	100 cc. water	20.89	.....	...	..
	37	15	0.65	Capsules, 100 cc. water	15.20	28 decrease	890	+2
	38	15	....	Capsules, 100 cc. water	15.60	26 decrease	914	+5
7. J. L., boy;	39	Control day		.....	21.68	.....	974	..
age, 7 yr.;	40	0	....	200 cc. tomato juice	21.74	.....	949	−3
weight, 23 Kg.;	41	10	0.43	200 cc. tomato juice	17.14	21 decrease	968	−1
height, 115 cm.	42	10	0.43	200 cc. water	21.62	.....	980	+1
8. W. S., boy;	43	Control day		.....	20.82	.....	907	..
age, 6 yr.;	44	0	....	200 cc. tomato juice	20.45	.....	...	..
weight, 18 Kg.;	45	10	0.56	200 cc. tomato juice	18.00	18 decrease	936	+3
height, 111 cm.	46	0	....	200 cc. water	20.34	.....	...	..
	47	10	0.56	Capsules, 200 cc. water	17.60	18 decrease	980	+9
9. N. R., boy;	48	0	....	200 cc. tomato juice	23.07	.....	908	..
age, 8 yr.;	49	10	0.42	200 cc. tomato juice	18.46	20 decrease	980	−2
weight, 24 Kg.;	50	0	....	200 cc. water	22.64	.....	...	..
height, 126 cm.	51	Control day		.....	22.85	.....	960	−4
	52	15	0.63	Capsules, 200 cc. water	15.86	31 decrease	...	..

illustrating the total salt effect is seen in the chart. The curve was obtained from the results in case 4, but it is typical of all the cases.

Studies of the basal metabolism were made for all experimental subjects by the method previously reported. On days when salt was given the tests were made during the phase of the maximum salt effect. The study of insensible loss of weight was necessarily curtailed as soon as this maximum effect appeared.

RESULTS

The results of our experiments are shown in the table. It may be seen that in every case in which salt was administered either in capsules or in tomato juice, the rate of insensible perspiration was decreased, the decrease varying from 15 to 31 per cent. Even the smallest dose of salt administered, 5 Gm. (0.23 Gm. per kilogram), was sufficient to effect a distinct physiologic change. When larger doses were administered to the same subject (cases 2, 3, 5 and 9) a greater decrease in the rate of insensible perspiration was noted. However, this decrease bore



Curve showing effect of salt on insensible perspiration. The level during the first hour represents the level on a control day.

no absolute quantitative relation to the increment in dose. For example, in case 2 there was a decrease of 20 per cent when 5 Gm. of salt (0.28 Gm. per kilogram) was given by capsule. When 10 Gm. (0.56 Gm. per kilogram) was administered in the same vehicle, the decrease was 25 per cent. Similarly, in case 5, 10 Gm. of salt in tomato juice (0.31 Gm. per kilogram) effected a decrease of 25 per cent in the rate of insensible loss of weight, while 15 Gm. (0.47 Gm. per kilogram) effected a decrease of only 27 per cent.

Again, a given dose of salt per kilogram of body weight, administered in the same vehicle, did not effect identical alterations in the rate of insensible loss in any two subjects. The results, however, roughly approximated each other. In case 2, for example, 5 Gm. of salt (0.28 Gm. per kilogram) administered in capsules effected a decrease of 20 per cent, whereas in case 3 the same dose (0.29 Gm. per kilogram) effected a decrease of only 16 per cent. Similarly, 10 Gm. of salt in capsules (0.56 Gm. per kilogram) administered to subject 2 caused a decrease of 25 per cent, while the same dose given to subject 8, who

had the same body weight, effected a decrease of only 18 per cent. These differences in results exceed the usual limits of experimental error. We must therefore accept the difference as due to individual response to the doses of salt administered. It is possible that the differences in response may have been due to differences in the rate at which the salt was absorbed, even when it was administered in the same vehicle.

We also considered the possibility that the different vehicles may have an influence either on absorption of the salt or directly on insensible perspiration, but no significant effect attributable to the vehicle could be demonstrated. Our material, however, is too limited to warrant any far reaching speculation on this phase of the problem.

Our data reveal that in all the subjects to whom salt was administered the reduction in the rate of insensible loss began about one and one-half hours after the administration and lasted about two hours. The results of tests of the basal metabolism made on days when salt was given remained practically the same as on control days. Salt in the doses administered did not affect the basal metabolism in any case.

COMMENT

Since we found that single doses of salt cause a decrease in the rate of insensible perspiration without influencing the total heat production, our results essentially corroborate for children the findings of Gilman and Barbour for their experimental animals. As the total energy metabolism remains unchanged the decreased rate of insensible perspiration must be otherwise accounted for. The explanation is in a large measure tied up with the concept of insensible perspiration.

Those who have considered insensible perspiration as a process of physical diffusion [12] may have reasoned that salt exerts a physical effect on the blood sufficient to increase its osmotic pressure and, as a result, to inhibit loss of fluids by vaporization. Since alterations in the volume of fluid in the body have been reported to influence insensible loss of weight,[13] and since salt is known to effect a temporary retention of body fluids,[14] it has been suggested that the fundamental effect of the

12. Hancock, W.; Whitehouse, G. R., and Haldane, J. S.: Proc. Roy. Soc., London, s.B **105**:43, 1929. Krause: Handwörterb. d. Physiol. **2**:131, 1844.

13. Erisman, F.: Ztschr. f. Biol. **11**:1, 1875. Dennig, A.: Ztschr. diätet. u. physik. Therap. **1**:281, 1898. Moog, A., and Nauck, E. T.: Ztschr. f. d. ges. exper. Med. **25**:385, 1921. DeRudder: Ztschr. f. Kinderh. **45**:404, 1928. Bratusch-Marrain, A.: Arch. f. Kinderh. **87**:81, 1929.

14. Cohnheim: Ztschr. f. Biol. **18**:129, 1898. Tuteur, R.: ibid. **53**:361, 1910. Joseph, D. R., and Meltzer, S. J.: J. Pharmacol. & Exper. Therap. **2**:282, 1911. Weech, A. A.; Goettsch, E., and Reeves, E. B.: Bull. Johns Hopkins Hosp. **58**:1, 1936. Widal, F., and Javal, A.: Compt. rend. Soc. de biol. **56**:436, 1904. Helmreich, E., and Schick, B.: Ztschr. f. Kinderh. **30**:147, 1921. Miller, J. L.: The Elimination of Chlorides in Nephritis, J. A. M. A. **45**:1915 (Dec. 23) 1905. Mackay, E. M., and Mackay, L. L.: Am. J. Physiol. **115**:455, 1936.

salt is to diminish the volume of fluid made available for vaporization through the skin and the lungs. However, considerable experimental evidence has been advanced to show that the effect of salt is primarily due not to a change in the volume of body fluids but rather to a change in osmotic pressure, and further that this change in osmotic pressure is the factor which controls the amount of water available for vaporization. Grüner [15] as early as 1907 showed that when a diet rich in salt is taken the osmotic pressure of the blood increases and there is then a decreased output through the skin, the lungs and the urine. Regnier [16] in 1916 confirmed these findings. The experimental work of Gilman and Barbour previously cited further corroborated this concept and emphasized the fact that extrarenal losses are dependent on the nature as well as on the volume of body fluids.

Certain authors have stated the belief that the mechanism of insensible perspiration is more closely related to subthreshold activity of the sweat glands.[17] According to this theory, the decreased rate of insensible loss must be due to a direct inhibitory action of the salt on secretion of the sweat gland.

That salt does exert such an inhibitory action on the secretions of the body is well known. Stookey,[18] Miller,[19] Hamburger,[20] Schutz [21] and Levites [22] demonstrated this action for gastric secretion. Krasnogorski [23] and his co-workers found this to be true for salivary and for pancreatic secretions. Krasnogorski, in fact, utilized the inhibiting effect of salt on secretion of the kidneys as a basis for his treatment of nocturnal enuresis.

Although the purely physical effect on the mechanism which regulates surface evaporation seems to afford the most logical explanation of the salt effect, we cannot gainsay that a direct depressant action on the sweat glands in certain regions of the body may be an augmenting factor.

The possibility that salt produces a temporary hydration of the liver and thus decreases the amount of fluid available for elimination through

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15. Grüner, O.: Ztschr. f. klin. Med. **64**:455, 1907.

16. Regnier: Ztschr. f. exper. Path. u. Therap. **18**:139, 1916.

17. Barratt, J. O. W.: J. Physiol. **21**:192, 1897. Moog, O., and Buchheister, K.: München. med. Wchnschr. **73**:398, 1926. Jurgensen, E.: Deutsches Arch. f. klin. Med. **144**:193, 1924. Cramer, E.: Arch. f. Hyg. **10**:231, 1890. Schwenkenbecher, A., and Spitta, O.: Arch. f. exper. Path. u. Pharmakol. **56**:284, 1907.

18. Stookey, L. B.: M. News, Feb. 14, 1903.

19. Miller: Arch. f. Verdauungskr. **1**:233, 1895.

20. Hamburger, W. W.: The Inactivation of Pepsin by Sodium Chlorid: Its Clinical Significance, Arch. Int. Med. **16**:356 (Sept.) 1915.

21. Schutz: Beitr. z. chem. Physiol. u. Path. **85**:406, 1904.

22. Levites, S. J.: Ztschr. f. physiol. Chem. **57**:46, 1908.

23. Krasnogorski, N. J.: Monatschr. f. Kinderh. **57**:252, 1933.

the skin and the lungs must also be borne in mind, although no proof of this is as yet available. Marshall, Aydelotte and Barbour [24] showed that when cocaine is administered to rabbits there follows a rise in temperature with a temporary decrease in insensible perspiration. These authors explained this decrease on the basis of an initial hydration of the liver, demonstrated when the animals were killed. Similar experiments with the use of salt to depress insensible perspiration might throw some light on this aspect of the problem.

Whatever the mechanism may be which results in a decrease of insensible perspiration after ingestion of salt, it is significant that total heat production remains unchanged. This further confirms the theory that insensible perspiration is concerned not only with regulation of heat, but with the state of body hydration.

Since homothermal animals normally maintain a constant body temperature, heat production equals heat elimination. It may be asked what happened to the heat conserved as a result of the decreased elimination which occurred during the salt effect in our experiments. This is a particularly pertinent question, since no demonstrable increase in body temperature occurred in any case. Apparently the body compensates easily for interference with its physiologic function of heat regulation. An inverse relation is known to exist between the proportions of heat liberated through the two principal channels, vaporization, and radiation and conduction. Any factor which influences in a certain way the proportion of heat eliminated by vaporization will necessarily have the opposite effect on the proportion dissipated by radiation and conduction, and vice versa,[25] if the body temperature is to remain constant.

In this connection, the work on variations in temperature gradients in the deeper tissues of the body must be of significance. It is recognized that heat gradients exist in man in zones, from the surface of the skin to various depths, and that these gradients vary throughout the body according to the circumstances of formation and loss of heat.[26] Although in our experiments temperatures were not recorded for the skin or for the deep tissues, it may be that the deeper tissues altered their temperature gradients in an attempt to compensate for the temporarily decreased elimination of heat through vaporization.

SUMMARY

In this study an attempt was made to determine the effect of single doses of salt on insensible perspiration. Hospital normal children were observed, and varying doses of salt were administered, either in gelatin

24. Marshall, H. T.; Aydelotte, B. F., and Barbour, H. G.: Am. J. Physiol. **98**:615, 1931.

25. Kriss, M.: Am. J. Physiol. **116**:262, 1936.

26. Sampson, J. J.: Am. J. Physiol. **117**:208, 1936. Bazett, H. C., and McGlone, B.: ibid. **82**:415, 1927.

capsules or in tomato juice. Preliminary studies showed that the vehicle itself was without influence on insensible perspiration.

A definite reduction in the rate of insensible perspiration could be effected in all cases. The immediate cause of the decrease in insensible perspiration can most logically be explained by the effect of the salt in increasing the osmotic pressure of the blood, which in turn effects changes in the vapor pressure of the fluids available for vaporization. The theory that the salt effect is primarily due to retention of fluids (increased volume) has been discussed but is considered less tenable. The possibility that the effect is augmented by a direct depressant action of salt on the secretory activity of the sweat glands cannot be gainsaid.

Whatever the mechanism causing the decrease in insensible perspiration, the fact that there was no change in total heat production confirms the conception that insensible perspiration is a function not only of heat regulation but of the state of tissue hydration.

The fact that no perceptible alteration in body temperature occurred, notwithstanding the decrease in loss of heat gives rise to the thought that a compensatory loss of heat through radiation and conduction may have taken place. The likelihood that alterations in the temperature gradients of the deeper tissues play an important role in heat regulation must be emphasized. It has previously been shown that in homothermal animals heat elimination equals heat production. Any interference with elimination through one channel therefore must necessarily affect the proportion eliminated through other channels.

ZINC SULFATE AND EXPERIMENTAL POLIOMYELITIS

EFFECT OF NASAL SPRAYS AFTER INTRAVENOUS INJECTIONS OF VIRUS

JOHN A. TOOMEY, M.D.
AND
WILLIAM S. TAKACS, B.S.
CLEVELAND

It has been suggested that poliomyelitis virus given intravenously is excreted along the area supplied by the olfactory nerve [1] and that Macacus rhesus monkeys thus inoculated contract the disease because the virus is reabsorbed by the end fibers of the first and thirteenth nerves, the virus being then carried to the central nervous system along the nerve fibers. It seems logical to suppose that after the virus is injected intravenously it is excreted not only along the region derived from the stomodeum, i. e., the nasal area, but also along the gastrointestinal tract. Instillation of a 1 per cent solution of zinc sulfate in the nasal area prevents poliomyelitis from occurring in experimental animals if the virus is subsequently introduced by way of the nose. If the virus is excreted only by the nasal route after being intravenously injected, zinc sulfate should prevent the disease in animals thus inoculated. The object of these experiments was to test this point.

METHODS

The experiments were carried out with treated and untreated Macacus rhesus monkeys. An animal to be treated was held in the upright position, and a 1 per cent solution of zinc sulfate was blown into both nostrils at such an angle that it would reach the olfactory area. The monkey was then turned upside down, and the nasal passages were again sprayed with a 1 per cent solution of zinc sulfate. A long, thin pipet was next inserted into the back of the nose, and more of the material was instilled. The first procedure should have been sufficient, but the second and third were added in order to make it absolutely certain that the zinc sulfate reached the olfactory area. These three procedures were carried out twice daily for two days prior to the inoculation and twice daily thereafter until

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From the Department of Pediatrics, Western Reserve University, and the Division of Contagious Diseases, City Hospital.

1. Lennette, E. H., and Hudson, N. P.: Relation of Olfactory Tracts to Intravenous Route of Infection in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **32**:1444, 1935.

treated animals contracted the disease. In every experiment a nontreated animal was used as a control for each treated animal. Since the dose of the virus varied in accordance with the size of the animal, monkeys of comparable weights were selected as far as possible. All injections of virus suspensions were made intravenously.

RESULTS

Animal 1, spray treated, and animal 2, control, were each inoculated with 10 cc. of a 10 per cent suspension of Flexner's M. V. strain on Jan. 17, 18, 19, 20, 23, 24 and 26, 1937. The spray-treated animal manifested poliomyelitis on January 27 and was killed on January 30. The control became sick on January 30 and was killed on January 31.

Animal 3, spray treated, and animal 4, control, were each inoculated with 10 cc. of a 10 per cent suspension of purified [2] Flexner's M. V. strain daily from March 7 to 17 inclusive. On March 18, animal 3 showed bulbar poliomyelitis and paralysis of the arms; it died that night. Daily injections were continued for animal 4 until March 29, but the disease did not develop. Some immunity must have developed in this animal, since it resisted three subsequent intracerebral injections of virus. It finally died of miliary tuberculosis.

Animal 5, spray treated, and animal 6, control, were each inoculated daily with 10 cc. of a 10 per cent suspension of purified Flexner's M. V. strain from March 30 to April 5, inclusive; 15 cc. of the same virus suspension was injected daily from April 6 to 8, inclusive; on April 9, 20 cc. was injected. On April 9, animal 6, the control, manifested bulbar paralysis as well as paralysis of both arms; it died the next day. Animal 5 was inoculated with 40 cc. of a 10 per cent unpurified virus suspension on April 12 and April 13. Quadriplegia developed on April 16, and the monkey died on April 17.

Animal 7, spray treated, and animal 8, control, were each inoculated daily for three days with 30 cc. of a 10 per cent suspension of Flexner's M. V. strain. In animal 7 weakness of the left leg developed, and it died suddenly on the sixth day after the last injection of virus. As it was not certain that this animal had the disease, animal 9 was substituted. On April 26 and 28 and on May 4 and 7 animals 8 and 9 each received 30 cc. of the same virus suspension. Animal 8, the control, manifested poliomyelitis on May 9, quadriplegia developing. It was killed on May 10. In animal 9 paresis of the left lower extremity and of the right arm developed on May 14.

Animal 10, spray treated, and animal 11, control, were inoculated intravenously on August 8, 10, 12 and 14 with 30 cc. of a 4 per cent virus suspension, and with 40 cc. on August 16, 18, 20, 21, 23 and 25. Animal 10 showed furring of the tongue and was inactive on August

2. Schaeffer, M., and Brebner, W. B.: Purification of Poliomyelitis Virus. Arch. Path. **15**:221 (Feb.) 1933.

20; it showed incoordination on August 23 and had paresis of the legs on August 30. Animal 11, the control, showed furring August 18; it had paresis of both feet on August 20 and paresis of both lower extremities on August 23. On August 30 it was more active and had only slight weakness of both legs.

Animal 12, spray treated, and animal 13, control, were inoculated intravenously with 30 cc. of a 4 per cent virus suspension (Flexner's M. V.) on August 8, 10, 12 and 14 and with 40 cc. on August 16. In animal 12, the protected one, there developed paralysis of both arms and weakness of the right leg as well as signs of bulbar involvement. It died of the infection on August 19. Animal 13, the control, had slight weakness of the legs on August 18, but did not become paralyzed at this time. It was inoculated with 30 cc. of the same virus suspension on August 21, 23 and 25. On August 23 both legs were definitely weak; on August 30 the paresis was more obvious; on August 31 both lower extremities were completely paralyzed, while the arms were only weak.

COMMENT

It is obvious from these experiments that blocking the nasal area with zinc sulfate does not prevent the disease when the virus is subsequently introduced intravenously.

Blocking the nasal area with a 1 per cent solution of zinc sulfate prevents the disease if the virus is introduced intranasally.[3] I confirmed this point in a few animals tested with controls. If an animal protected in the nasal area and subsequently inoculated intravenously with poliomyelitis virus contracts the disease, the virus must come in contact with gray fibers at some place other than the olfactory area. It seems logical to suppose that if the virus is excreted along the region derived from the stomodeum, it might be excreted along the entire gastrointestinal tract. It seems illogical that virus injected intravenously would be excreted only by way of the olfactory area. Whether it can be isolated from the intestine in animals thus treated will be made the subject of further communications.

It seems obvious that there are variabilities in resistance to infection, so that a certain intravenous dose of virus might produce the disease in one animal and not in another. In a few animals this difference might lead to erroneous conclusions so definitely that the experiment might be considered conclusive. The factor of a monkey's normal resistance is not given its proper due in experiments with intravenous injections of the virus.

3. Schultz, E. W., and Gebhardt, L. P.: Olfactory Tract and Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **31**:728, 1934.

Since the minimal intravenous dose which can produce disease is unknown, it is extremely difficult to compare animal with animal. The fate of the animal must depend in some measure on its well-being. This point will be enlarged on later, but it has become obvious to me that not only must the monkeys be comparable in weight, but they must have had an adequate diet and the periods of observation must be about equal for all. It is impossible to compare a poorly fed and rachitic monkey with one that is well nourished and well developed, especially if the latter has also had all the necessary vitamins.

CONCLUSION

Macacus monkeys treated intranasally with a 1 per cent solution of zinc sulfate contracted poliomyelitis when the virus was injected intravenously.

HYPOTHYROIDISM AS A CAUSE OF DISEASE OF THE HIP

BERNARD BENJAMIN, M.D.
AND
PHILIP R. MILLER, M.D.
BROOKLYN

Endemic cretinism in the adult is often accompanied by a variety of skeletal malformations. The victims of this disorder characteristically exhibit poor posture, with the head inclined forward and with the hips, knees and ankles maintained in partial flexion.[1] Their gait is such as to give the observer an impression of marked instability. One of the factors contributing to the instability is the disturbance of the mechanics of pelvic support resulting from relaxation of the pelvitrochanteric musculature. This in turn arises from the presence of coxa vara, a deformity which is frequently encountered in cretins.[2]

The osseous changes appearing in children and resulting in the development of coxa vara in cretins have received scant attention. But few reports on the subject have appeared and these have been limited to the Swiss and German literature. In them the authors have described the occurrence of a disease of the hip resembling the osteochondritis of Legg, Calvé and Perthes. So far as the phenomena affect the sporadic cretins of regions in which goiter is not endemic the problem appears to have been overlooked almost entirely.

The first clinical report demonstrating the presence of abnormal ossification of the head of the femur in a cretin child was made by Läwen in 1909.[3] It is interesting to note that it appeared just before the published accounts of Legg, Calvé and Perthes on osteochondritis of the capital epiphysis of the femur. Several years later Roth [4] briefly described three cases of "Perthes' coxitis deformans juvenilis" occurring in two young cretins and one cretinoid adult. This was followed by the account published by von Seemen,[5] which included descriptions

From the Department of Pediatrics of the Jewish Hospital.

1. Flinker, A.: Studien über Kretinismus, Vienna, Franz Deuticke, 1930.

2. Bircher, E.: Die Entwicklung und der Bau des Kretinenskeletts, Fortschr. a. d. Geb. d. Röntgenstrahlen (supp.) **21**:1, 1909.

3. Läwen, A.: Zur Kenntnis der Wachstumsstörungen am Kretinenskelett, Deutsche Ztschr. f. Chir. **101**:454, 1909.

4. Roth, O.: Berichte der Gesellschaft der Aerzte des Kantons Zürich, Cor.-Bl. f. schweiz. Aerzte **48**:951, 1918.

5. von Seemen, H.: Osteochondropathia cretinoidea, Arch. f. klin. Chir. **152**: 616, 1928.

of two children with hypothyroidism who showed abnormal ossification of the femoral heads. More recently, Brailsford [6] mentioned one such case in a monograph, while Looser [7] summarized a larger experience based on pathologic and clinical material from one of the Swiss districts where goiter is endemic.

Our interest in the subject was aroused when we encountered a case of slipped epiphysis in a boy who showed the characteristic stigmas of hypothyroidism. Although it appeared possible that his hypothyroid state might have been responsible for the femoral disease, we learned that no such etiologic relationship is recognized.[8] We were able, however, to discover an isolated observation of some interest. In 1928 Lewin [9] reported the case of a 9 year old girl whose hips revealed an unusual roentgenographic shadow at the lower margin of the capital epiphysis of the femur. The abnormal structure had the appearance of being either an adventitious bone or a split-off portion of the femoral head. The author incidentally mentioned the fact, pertinent to the present study, that the patient had slipped epiphysis bilaterally and that she was a cretin.

In view of the roentgenographic changes found in Lewin's case, as well as in our own, it seemed important to investigate the status of the development of the hips in other children manifesting evidences of hypothyroidism. It was possible to study seven additional cases. The children ranged in age from 4 to 12 years and had been under observation at the clinic over an extended period. Five were boys and two girls. The diagnosis of hypothyroidism in all cases was thoroughly established by means of the history, physical examination, determination of the rate of osseous development of carpal centers of ossification as shown by roentgenograms, blood cholesterol values and physical and mental progress under thyroid medication. Although determination of the basal metabolic rate was regularly carried out, it was impossible to place great reliance on the results. This was due in part to the frequently encountered difficulty in obtaining satisfactory cooperation from the children and in part also to the confusing variety of published normal standards. None of the children had complained of symptoms referable to the hips, and in none had hip disease been suspected.

Roentgenographic study of the children failed to reveal additional instances of slipped epiphysis but did bring to light three cases of

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6. Brailsford, J. F.: The Radiology of Bones and Joints, ed. 2, Baltimore, William Wood & Company, 1935, p. 214.

7. Looser, E.: Die Kretinenhüfte, Schweiz. med. Wchnschr. **59**:1258, 1929.

8. Bircher [2] postulated the occurrence of displacement of the capital epiphysis to account for the development of coxa vara in cretins. He was unable, however, to demonstrate such a lesion in an actual case.

9. Lewin, P.: An Unusual Roentgenographic Finding in the Hip, Am. J. Roentgenol. **19**:290, 1928.

bilateral osteochondrosis of the head of the femur. These, together with the case of the first boy who came under our observation, form the basis of the present report.

REPORT OF CASES

CASE 1.—F. B., a boy aged 11 years, was brought to the outpatient department because of a limp of the left leg. About three months previously he had fallen from a bicycle, injuring his left hip, and in consequence was confined to bed for three weeks. When he was allowed out of bed he began to limp and complained of pain in the left hip. His family history was unimportant. There had been no exposure to tuberculosis. At birth he appeared to be normal and weighed about 10 pounds (4,536 Gm.). However, he failed to show satisfactory physical and mental progress, and for many months feeding was very difficult. Retardation of development was shown in his failure to hold his head up for several months and inability to sit until he was 1 year old and to walk until he was 2 years old. He could not talk until he was 3 years of age. The nature of his difficulty was not appreciated until he was 17 months old, at which time his mother was informed that the infant was a cretin. Thyroid medication (the exact dose is unknown) was prescribed and was followed by rapid and striking improvement in his general condition. His development proceeded normally after this, and he was able to attend school and to advance satisfactorily. About three years before his present illness treatment with thyroid tablets became intermittent and irregular. During this period his mother noticed that withholding his medication resulted in his becoming sluggish and its resumption was followed by a return to a more alert state. About a year before his fall, treatment was stopped entirely.

Examination revealed a stunted but apparently intelligent boy of 11 years, measuring 50½ inches (128 cm.) in height and weighing 61½ pounds (28 Kg.) (the average figures for his age are 56 inches [142 cm.] and 77 pounds [34 Kg.], respectively). His skin was very dry and scaly and showed a pasty yellow color. A characteristic facies, together with a saddle nose, coarse, straight hair, short, spadelike hands and a harsh, rasping voice, strongly suggested hypothyroidism. The thyroid gland was not palpable. There was no fever, and except for the disability of his left leg he did not show any constitutional signs of disease. There was no wasting of the left thigh, but orthopedic examination by Dr. M. T. Koven revealed definite limitation of motion of the left hip, chiefly in abduction and internal rotation but to a certain extent in flexion. Roentgenograms of his hips revealed in the anteroposterior view a slight medial displacement of the left capital epiphysis and an irregular shadow of the upper portion of the neck of the femur (fig. 1). The appearance was suggestive of an epiphysis which had slipped posteriorly and was casting a roentgenographic shadow superimposed on that of the neck. This impression was substantiated by a lateral view taken with the hip in abduction (fig. 2). The right femoral head showed broadening of the epiphysial line. The roentgenogram of the wrists revealed only six carpal centers of ossification on the right and seven on the left and failure of ossification of the distal epiphysis of the ulna on each side (fig. 3). Except for numerous transverse lines in the long bones and a possible early humerus varus deformity, roentgenographic study of the rest of the skeleton showed no striking abnormalities. Laboratory investigations yielded the following results: The Kline test was negative. The tuberculin reaction was negative with amounts up to 0.1 mg. The blood cholesterol content was 786 mg., per hundred cubic centimeters, the serum calcium content 10.3 mg., the phosphorus content 4.5 mg. and the value for phosphatase

2.5 Bodansky units. The curve for the blood sugar content after the ingestion of 47 Gm. of dextrose was relatively flat, with a maximum rise to 151 mg. per hundred cubic centimeters from a level during fasting of 125 mg. Two weeks after the daily administration of 1 grain (0.06 Gm.) of desiccated thyroid was begun, the blood cholesterol content had fallen to 340 mg.

Because the condition was too far advanced for more satisfactory procedures treatment adopted by the orthopedic department was conservative, consisting in the application of a plaster spica cast and, after its removal several weeks later, the use of a brace to protect the hip from weight bearing. Roentgenograms taken after five months showed moderately advanced secondary destructive changes in the displaced epiphysis.

CASE 2.—W. S., a boy aged 9 years, was first seen in the outpatient department in October 1928, when he was 1 year old. He was brought for examination

Fig. 1 (case 1).—Roentgenograms of the hips, showing slight medial displacement of the capital epiphysis of the left femur (Whitman's sign). The diagnosis of slipped epiphysis was confirmed in the lateral view of the hip (fig. 2). Increased prominence of the line representing the lower border of the right capital epiphysis may also be noted here.

at this time because his back was very much bowed in the sitting position and because he was unable to sit without support. He seemed healthy at birth, his weight being 9 pounds and 12 ounces (4,423 Gm.) but he failed to develop in a normal manner. Examination at 1 year of age disclosed generalized hypotonia, a yellowish tint to the skin, pot belly with an umbilical hernia, a widely open fontanel and absence of teeth. A blood count showed hemoglobin 49 per cent (Sahli), 2,400,000 red cells and 7,200 white cells, with 33 per cent polymorphonuclear neutrophils, 63.5 per cent lymphocytes and 3.5 per cent monocytes. The reaction to tuberculin was negative in a series of tests with amounts up to 5 mg. The infant was thought to be suffering from rickets. Hypothyroidism was not suspected at first, but a few months later administration of thyroid tablets

(½ grain [0.03 Gm.] daily and later 1 grain [0.06 Gm.] daily) was begun, and this was followed by improvement in the child's condition. He became much more alert and active and appeared more intelligent to the examining physician.

Fig. 2 (case 1).—Lateral view of the left hip, showing marked slipping of the capital epiphysis posteriorly and downward. The inadequacy of the anteroposterior view (fig. 1) in demonstrating the extent of epiphysial displacement is evident from a comparison of the two roentgenograms. The pelvis in this photograph is at the top of the figure, its vertical axis rotated almost to the horizontal position.

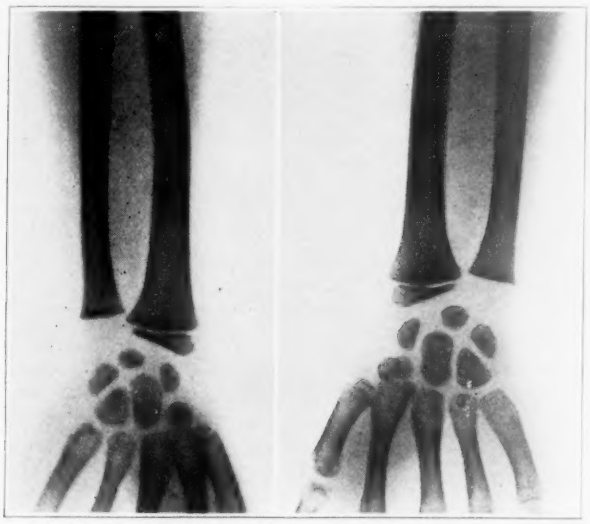

Fig. 3 (case 1).—Roentgenogram of the wrists of the patient at 11 years of age. Retardation of epiphysial development is visible not only in the carpal centers but also in the failure of ossification of the distal epiphysis of the ulna, a structure which normally undergoes bony transformation during the seventh year.

The first teeth erupted at 20 months. He began to walk and to talk when he was 2½ years old.

After January 1930 the child was not brought to the clinic again for almost a year. He was then 3 years of age but was found to have only sixteen teeth. He was moderately constipated. There were no other complaints. He was not seen again until February 1936, at which time he was 8 years of age. During the latter two and a half years of the interval since his last visit he underwent treatment for hypothyroidism at another hospital. During this period he sustained a spiral fissure fracture of the left tibia, from which he made a good recovery. On his return to the clinic roentgenograms of his wrists were taken. There were visible only four well developed carpal centers of ossification, with a tiny shadow representing the fifth (fig. 4). The distal epiphysis of the ulna was not ossified. The boy was now 47 inches (119 cm.) tall and weighed 59 pounds (27 Kg.) (the average figures for his age are 50 inches [127 cm.] and 58 pounds [26 Kg.], respectively). His blood cholesterol content was found to be 260 mg.

Fig. 4 (case 2).—Comparison of development of the wrist at 8 years of age (left) and eight months later (right), after an interval of increase in the dose of thyroid.

per hundred cubic centimeters, and hematologic examination revealed the presence of slight hypochromic anemia. Therapy with thyroid tablets had been most irregular, and his mother had repeatedly observed that discontinuance of medication was always followed by sluggish behavior. The patient was in the first grade in school and had several times failed to be promoted. His intelligence quotient was 86, his chronological age 8 years and 5 months and his mental age 7 years and 3 months. It was obvious that more intensive treatment was urgently needed in his case. Accordingly, thyroid in increasing doses up to 3 grains (0.2 Gm.) daily was ordered and this level maintained for the next eight months. At the end of this time roentgenograms of his wrist were again taken. Seven carpal centers were now present, although three were still small. Ossification of the distal epiphysis of the ulna, which normally commences during the seventh year of life, was still absent (fig. 4). A considerable degree of bony growth was evident from a comparison of the position of the transverse lines with that in the previous plates. The boy had grown 2 inches (5 cm.) taller, and his weight had remained stationary.

During the course of his visits to the dispensary it was noted that he walked with a peculiar gait. A mild talipes varus deformity was found and suitable shoes prescribed, but the difficulty was not thus corrected. A roentgenographic study was made to investigate the hips for possible disease. The plates showed flattening of the capital epiphysis of the left femur, as well as a mottled appearance that suggested an abnormal bony structure (fig. 5). The neck appeared to be widened and showed some irregularity of architecture. The disordered structure of the metaphysial region was well seen in the lateral view (fig. 6). The right capital epiphysis presented a more normal contour, but the regular trabecular architecture was lacking. A mottled roentgenographic shadow similar to, but not so pronounced as, that on the left side was noticeable. The changes found seemed out of proportion to the clinical appearance of the patient. An orthopedic examination was made by Dr. J. E. Milgram, whose note follows: "The child walks with a left-sided

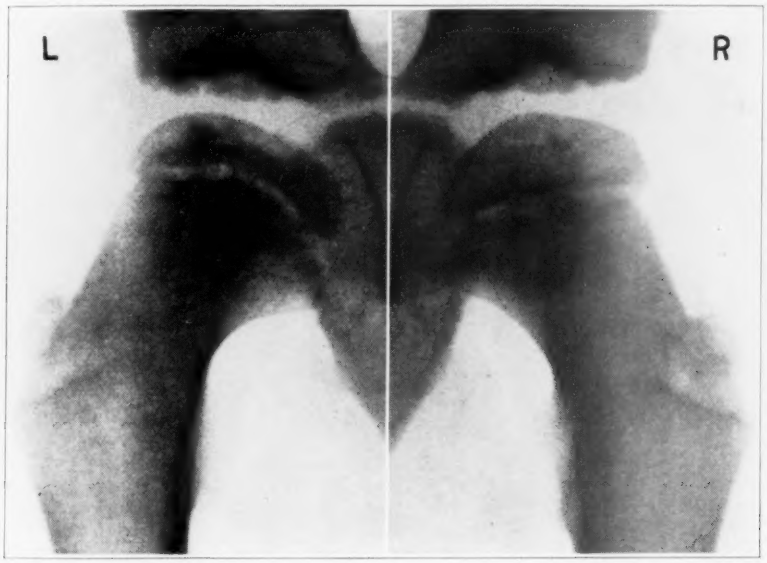

Fig. 5 (case 2).—Anteroposterior view of the hips, showing marked flattening and irregularity of ossification of the left capital epiphysis as well as less advanced changes on the right side.

limp due to a ⅜ inch [0.9 cm.] shortening of the left leg. This occurs above the knees, since the tibias are of equal length. There is marked loss of internal rotation of the left hip, with slight loss of abduction. A 10 degree flexion contracture of the left hip is present. The ranges of motion are as follows: Flexion is full. Adduction on each side is 40 degrees. Abduction on the right is 50 degrees and on the left 40 degrees. Internal rotation on the right is 40 degrees and on the left 15 degrees. External rotation on the right is 45 degrees and on the left 45 degrees. The patient walks peculiarly, with an inelastic gait, the right foot being held in a slight varus position and coming down with a thud at each step. The Trendelenburg test is negative bilaterally."

Orthopedic examination of motion at the hips, therefore, showed essentially the presence of marked left-sided limitation of internal rotation as well as some limitation of extension and abduction on the same side.

Roentgenographic study of the remainder of the osseous system revealed little of interest.

Although improvement in the patient's general condition resulting from the thyroid medication was readily observable, a similar favorable response in the condition of the hip failed to occur. The patient began to have subjective symptoms referable to his left hip. He cried nightly because of the pain, and he often limped on becoming fatigued. It was suspected that he was suffering a progressive fragmentation of the head of the femur as a result of the repeated impacts connected with weight bearing. Complete rest in bed for a period of six months in a home for convalescents was ordered.

CASE 3.—M. S., a boy aged 6 years, was observed in the outpatient department since he was 27 months old. At that time the chief complaint was failure to talk or walk. There were no illnesses in the family, and his five brothers and

Fig. 6 (case 2).—Abnormality of structure of the head of the left femur as seen in the lateral view.

sisters were normal. He appeared to be normal at birth, but his subsequent development was retarded. He was unable to sit unsupported until he was 9 months old, and at the time of admission to the clinic was still unable to walk except when holding on to chairs. Talking was very limited. His appetite was poor; he was easily fatigued and spent an unusual amount of time in sleeping. Examination disclosed a poorly developed infant measuring 31 inches (79 cm.) in length (the average normal length for his age is 34 inches [86 cm.]) and weighing 27½ pounds (12.4 Kg.). The facial expression was stupid, the hair was thin, and the skin was dry. He had a large tongue and a pot belly. The impression of the examining physician was that the patient was a cretin. He failed to return for treatment until he was 3 years old. At this time he appeared mentally retarded and had made almost no progress in walking or talking. A roentgenogram of his wrist revealed only two carpal centers of ossification. Chemical determinations on the blood were made, with the following results: The cholesterol content was 300 mg. per

hundred cubic centimeters, the calcium content 9.1 mg., the phosphorus content 4.7 mg., the sugar content 78 mg., the value for chlorides 369 mg., the calcium dioxide combining power 53.8 volumes per cent, the total protein content 6.98 per cent and the nonprotein nitrogen content 32.5 mg. per hundred cubic centimeters.

Treatment with thyroid tablets was instituted and was followed by considerable improvement in the child's condition. The dose varied from time to time, but for a period of two and a half years was in the neighborhood of 1½ grains (0.09 Gm.) daily. He soon began to walk better and talked fairly well. Bony development, however, failed to keep pace with other clinical manifestations of progress. Nine months after the beginning of treatment, at the age of 3 years and 9 months, his wrists still had but two ossified carpal bones. Twenty months after therapy was started, when he was more than 4½ years, roentgenograms of his wrists showed four centers of ossification on one side and three on the other. Cooperation on the part of the mother in the execution of the medical program

Fig. 7 (case 3).—Roentgenogram of the wrist of the patient at 6 years of age. Until the boy was almost 4 years old only two carpal centers were visible. Two additional centers appeared during the fifth year. Ossification of the fifth, sixth and seventh carpal bones occurred during the sixth year, when thyroid medication was more intensive.

was not ideal, and periods of as long as two months without thyroid medication are recorded in the history. In December 1936, when the boy was 6 years old, roentgenograms of his hips were taken. His wrists at this time contained seven centers of ossification (fig. 7), and the cholesterol content of his blood was 231 mg. per hundred cubic centimeters. He appeared somewhat retarded mentally. For about a year the dose of thyroid had been 3 grains (0.2 Gm.) daily taken five days each week. There were no complaints referable to the lower extremities, and no disability had been noted. It was rather surprising to find roentgenographic evidence of a lesion involving both femoral heads (fig. 8). The epiphyses were flattened and presented an irregular mottled appearance instead of the normal trabecular markings. A large area of rarefaction was noticeable in the left femoral head. The epiphysial lines, particularly the left, were very irregular, and in this region there appeared to

be isolated areas of bone completely surrounded by cartilage. The pathologic appearance was even more striking in the lateral view of the hip (fig. 9). An orthopedic consultation was requested and the following report received: "There is a 15 degree loss of terminal internal rotation and of terminal extension of the left hip. A 3 to 5 degree flexion contracture is present on the left when the extremity is tested in some internal rotation. The motions of the right hip are full, free and painless."

CASE 4.—G. C., a boy aged 6 years, was under medical care for cretinism since early infancy. He was the only child of normal parents. He was born at term by cesarean section, weighed 10 pounds and 4 ounces (4,649 Gm.) and was 20 inches (51 cm.) long. Two weeks after birth he had "spasms of both legs," and his mother noticed that his face and body were abnormally puffy. At 4 weeks of age the presence of a protruding tongue and an umbilical hernia, as well as his general appearance, were typical enough to suggest a diagnosis of cretinism. On

Fig. 8 (case 3).—Anteroposterior view of the hips, showing moderate flattening and abnormal trabecular architecture of the femoral capital epiphyses.

appropriate therapy consisting of thyroid in doses up to 1½ grains (0.09 Gm.) daily he made fairly good progress, and at 6 months he measured 26 inches (66 cm.) in length. He was noted to have a wide nose with prominent nostrils and a depressed nasal bridge. Because of probable toxic symptoms thyroid medication at this time was reduced to ½ grain (0.03 Gm.) daily. This was followed by definite retardation in growth and development. The patient was unable to sit alone until he was almost 12 months of age, and for about a year after this dorsolumbar kyphosis was repeatedly noted. After the age of 14 months the dose of thyroid varied between 1 and 2 grains (0.06 and 0.1 Gm.) daily. The patient walked when he was 19 months old and began to talk at about the same time. Dentition and osseous development were delayed, and although the first tooth appeared during the ninth month, he had only ten teeth at 23 months, and his anterior fontanel was still open. At the age of 4 years his blood cholesterol content was found to be 286 mg. per hundred cubic centimeters.

At 6 years of age he was admitted to the hospital for review of his physical and mental status. He was quite obese, his weight being 67 pounds (30 Kg.) and his height 43 inches (109 cm.) (the average weight and height for his age are 45 pounds [21 Kg.] and 45 inches [114 cm.], respectively). His thyroid gland was

Fig. 9 (case 3).—Lateral view of the left hip, showing more pronounced areas of rarefaction in the capital epiphysis than are visible in figure 8.

Fig. 10 (case 4).—Roentgenogram of the wrist of the patient at 6 years of age. In addition to the delayed carpal development one notes the presence of numerous transverse lines in the distal portion of the radius.

not palpable. The genitalia were well developed. A small umbilical hernia persisted. He appeared to be alert mentally, and a Binet-Simon test showed an intelligence quotient of 103 and a mental age of 6 years and 10 months; the chronological age was 6 years and 7 months. The Kline test and the tuberculin reaction with 0.1 mg. of tuberculin were negative. Roentgenograms of the wrists revealed ossification of four carpal centers (fig. 10). Chemical studies of the blood showed the cholesterol content to be 241 mg. per hundred cubic centimeters, the calcium content 10.6 mg., the phosphorus content 4.1 mg., the value for phosphatase 6.9 Bodansky units, the sugar content 85 mg., the value for chlorides 351 mg., the total protein content 7.51 per cent and the albumin-globulin ratio 1.32. Thyroid therapy was stopped for a period of seven weeks. At the end of this time the blood cholesterol content had risen to 858 mg. per hundred cubic centimeters. On resumption of the treatment (from 3 to 4 grains [0.2 to 0.25 Gm.] thyroid daily) the value for

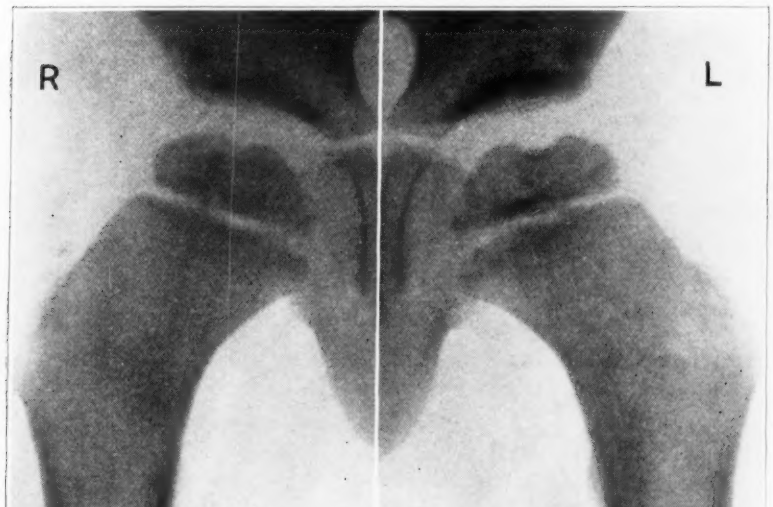

Fig. 11 (case 4).—Roentgenogram of the hips taken in the anteroposterior direction. Changes similar to those seen in figure 8 are noticeable.

cholesterol fell rapidly and at the end of one month returned to a level ranging from 175 to 218 mg. Satisfactory tests of the basal metabolism were possible in this case, and the results showed that the rate during this period rose progressively from —45 to + 3 per cent.

Roentgenographic study of the boy's hips revealed changes similar to those observed in the previous cases (fig. 11). The capital epiphyses showed moderate flattening, as well as a striking irregularity of contour. A mottled appearance contrasted with the normal markings of neighboring bony structures. The necks of the femurs were short, stubby and rather infantile in shape. Fraying of the trochanteric epiphyses was present.

An orthopedic examination was made by Dr. J. E. Milgram, who wrote the following report: "When the patient walks the rhythm of foot impact is not uniform and the left foot points inward. The left hip shows slight limitation of

internal rotation (about 10 degrees). With the hip flexed 90 degrees, however, a loss of 50 degrees of internal rotation is observed. Slight limitation of flexion (5 degrees) is present. When abduction is tested in the extended position the left hip lacks 15 degrees of motion as compared with the opposite side. A 15 degree flexion contracture of the left hip can be demonstrated, and extension past this position is not possible. On the right side internal rotation appears to be less than in the average patient of this age. Flexion is normal. There is extension to the neutral position but no hyperextension. External rotation on each side is apparently normal. The Trendelenburg test is positive on the right and suggestive on the left, indicating disturbance of the pelvitrochanteric musculature."

COMMENT

Clinical Data.—All the children in this series were suffering from the sporadic form of congenital hypothyroidism. They were unduly large at birth. In one case a cretinous appearance made possible the correct diagnosis at the age of 4 weeks. With the exception of this infant, in whom prompt treatment modified somewhat the course of the illness, all the children displayed marked retardation of physical and mental development during early life. When the children were given thyroid substance by mouth, accelerated physical and mental progress was regularly noted. When the medication was for one reason or another withheld, the patients relapsed into sluggish, apathetic ways. In each case the diagnosis of hypothyroidism was made long before the present investigation was begun.

It is noteworthy, however, that in none of the cases was the treatment entirely satisfactory. Two of the children had gone for years with little or no medication; a third suffered through lack of cooperation, while in the fourth regulation of the dose of thyroid was rendered difficult because of the readiness with which toxic symptoms appeared. All were short in stature and presented continued evidence of delayed epiphysial ossification as well as varying degrees of abnormality of cholesterol metabolism at the time the disease of the hip was discovered.

An attempt to evaluate the general incidence of the different forms of disease of the hip associated with hypothyroidism is beset with a number of difficulties. Bircher,[10] in a pathologic study of ten adult cretins, noted the presence of coxa vara in about half and commented on the fact that he had frequently observed this deformity in roentgenograms in clinical cases of cretinism. His material presumably consisted of untreated subjects. In recent years early diagnosis of the hypothyroid state and the more widespread use of thyroid medication may have modified these figures. The problem is further complicated by the fact that coxa vara is a deformity which may begin in a variety of ways and may have its origin in disease of the epiphysis, the epiphysial plate,

10. Bircher, E.: Ueber eine der Coxa vara entsprechende Difformität der Schulter (Humerus varus) bei Kretinen, Deutsche Ztschr. f. Chir. **96**:598, 1908.

the neck or the trochanters. Moreover, as Key [11] has stated, "In adult cases, due to loss of the epiphyseal line and progressive changes in the head and neck, it may be absolutely impossible to determine whether the original condition was a Legg's disease (*capital*) or an *epiphyseal* coxa vara." It therefore becomes necessary in analyzing the hip disease of persons with hypothyroidism to study the condition in childhood during its formative period. This is particularly true since in the present instance our experience has demonstrated the existence of two distinct types, the one a capital coxa vara due to osteochondrosis of the epiphysis proper, and the other an epiphysial coxa vara due to abnormality of the epiphysial plate. If one then considers only those cases occurring in children there are available descriptions of eleven patients, including our own. Of these, nine showed osteochondrosis of the head of the femur, and two had slipped epiphyses. The possibility of a combination of the two lesions of course exists, and one is led to suspect that this may have been so in Lewin's [9] case.

Slipping of the capital epiphysis of the femur is much more common in boys than in girls.[11] Similarly, the osteochondritis of Legg, Calvé and Perthes affects boys in overwhelming preponderance.[12] All the patients in our series were boys, but it is obvious that the published data on hip disease associated with hypothyroidism are insufficient to warrant conclusions regarding its relative frequency in the two sexes. It may be mentioned that Läwen's [3] patient and Lewin's,[9] as well as two described by von Seemen,[5] were girls. In the present study the ages of the children manifesting the osteochondrosis were 9, 6 and 6 years, respectively, while the boy with the slipped epiphysis, in accord with the somewhat higher age incidence of the latter disease, was 11 years of age.

A few observations regarding the clinical features exhibited by the patients reported on here may be worthy of mention. In the case of slipped epiphysis there was an abrupt onset due to a fall, and the condition was therefore not of the more common insidious type. Nevertheless, the trauma was not severe and would probably not have been sufficient to produce a similar lesion in a normal hip. The child had moderate pain, walked with a limp and was found to have typical limitation of motion at the hip, chiefly in abduction. The disability was detected by roentgenograms, which at the same time revealed in the opposite hip the presence of a widened capital epiphysial line of the type seen in the "preslipping stage." It is interesting to note that an anteroposterior view of the more involved side showed only slight displacement of the

11. Key, J. A.: Epiphyseal Coxa Vara or Displacement of the Capital Epiphysis of the Femur in Adolescence, J. Bone & Joint Surg. **8**:53, 1926.

12. Legg, A. T.: Osteochondral Trophopathy of the Hip-Joint, Surg., Gynec. & Obst. **22**:307, 1916.

epiphysis (fig. 1). This was due to the fact that the epiphysis had moved almost directly posteriorly and downward so that the displaced portion was overshadowed by the presence of the neck. The disturbed position of the head was more clearly shown in the lateral view (fig. 2). The photograph in this instance was taken with the hip in an attitude of flexion, abduction and internal rotation, and the resulting relationships of various landmarks in the plate are different from the accustomed ones. The flexion and internal rotation have projected the image of the greater trochanter upward and medially with respect to the neck, rendering it visible as a shadow nearer the head, obscuring the markings of the neck and extending somewhat beyond its lower border. The lesser trochanter is now the more prominent structure as it extends from the lower surface of the femur.

The three children with capital osteochondrosis showed bilateral involvement of varying severity. In each instance the process was considerably more advanced on the left side. In contrast to the patient in case 1, they were largely symptomless. Their gait, which is difficult to describe, had an inelastic and rather careless, shuffling character. This could not, however, have been entirely due to hip disease, since some of the patients with hypothyroidism but with roentgenographically normal hips displayed peculiarities of walking. By means of careful orthopedic examination it was possible to detect some disability in the affected joints. Well marked limitation of internal rotation and lesser degrees of limitation of abduction and of extension were found. The patient with the most advanced condition manifested shortening of the extremity as well as fatigability and spontaneous pain. Some of the less severely affected hips showed no limitation of motion whatever. In each instance the presence of the disorder was established by means of roentgenograms.

Despite variations in the degree of involvement of the hips, the osteochondrosis presented a more or less uniform roentgenographic picture. The capital epiphysis was seen as a small, flattened structure resting on a short, wide neck. The appearance resembled that of the caplike deformity of Legg-Calvé-Perthes' disease. In the most advanced case beginning "mushroom" form was present (fig. 5). The convex bony margin of the epiphysis manifested an interesting deviation from the normal. Instead of a smooth contour, an uneven wavy outline (fig. 11) and in some instances an actual break in continuity (fig. 6) could be discerned. The internal osseous structure likewise gave evidence of having undergone extensive pathologic alteration. The trabecular architecture was marred by variations in density, giving one the impression of widespread structural disorder. Areas of rarefaction of irregular shape and often of considerable size were present (fig. 9). These alternated with areas of increased density of ill defined form. The cartilagi-

nous zone separating the epiphysis from the neck was in turn much modified in aspect. The line in the films representing this region was in some places so altered as to present an angulated appearance (fig. 9). In other places it was widened to enclose what seemed to be islands of independent bony tissue.

The question in the three cases of the responsiveness of the osteochondrosis to treatment must be left largely unanswered for the present. In case 3 a second roentgenogram, taken after six months, showed moderate improvement. In case 4 roentgenograms taken after a similar interval of intensive therapy failed to show much change in the condition of the hips.

Pathologic Changes.—Consideration of the profound disturbance of ossification resulting from lack of function of the thyroid gland makes possible a clearer understanding of the hip disease presented in this study. Bony growth in hypothyroidism is much retarded, and cretins are consequently dwarfed. Delay in the appearance of centers of ossification and in the bony union of epiphysis to diaphysis is so characteristic of this condition as to be of diagnostic importance. There occur, however, other less generally known abnormalities of osseous development which are of more immediate concern in the present connection. These involve two separate sites: first, the epiphysial plate and, second, the epiphysis proper.

Many years ago Langhans,[13] in a study of cretinism, observed the presence at the epiphysiodiaphysial junction of an abnormal layer of bone, to which he applied the term *Querbalken.* This was seen in sections as a line of bony trabeculae lying transverse to the long axis of the bone and to the normal axial direction of the remaining trabeculae of the spongiosa. Langhans found that this layer of bone not only was detectable histologically but had sufficient density to be visible as a transverse line in a roentgenogram of the upper end of the tibia and fibula of a 35 year old cretin. His observations were elaborated in a study by Dieterle[14] of the bones of an infant with hypothyroidism who died at the age of 4 months. This author ascribed the phenomenon to a diminution in activity of the marrow, resulting from the lack of thyroid substance.

According to Dieterle, the resting cartilage showed little change other than a moderately diminished cell content. More marked changes occurred in the zone of proliferating cartilage, which was much dimin-

13. Langhans, T.: Anatomische Beiträge zur Kenntnis der Cretinen, Virchows Arch. f. path. Anat. **149**:155, 1897.

14. Dieterle, T.: Die Athyreosis, unter besonderer Berücksichtigung der dabei auftretenden Skelettveränderungen, sowie der differential-diagnostisch vornehmlich in Betracht kommenden Störungen des Knochenwachstums, Virchows Arch. f. path. Anat. **184**:56, 1906.

ished in width, its layer of hyperplastic cells measuring only 70 microns in width, as compared with a normal width of 230 microns. The cells were relatively few in number and exhibited a tendency to become arranged in a transverse rather than an axial direction. The increased matrix in this area was well calcified, and it was here that the most striking anomaly of osseous development was to be seen. Instead of a lattice-work of calcified matrix broken up through the erosive action of

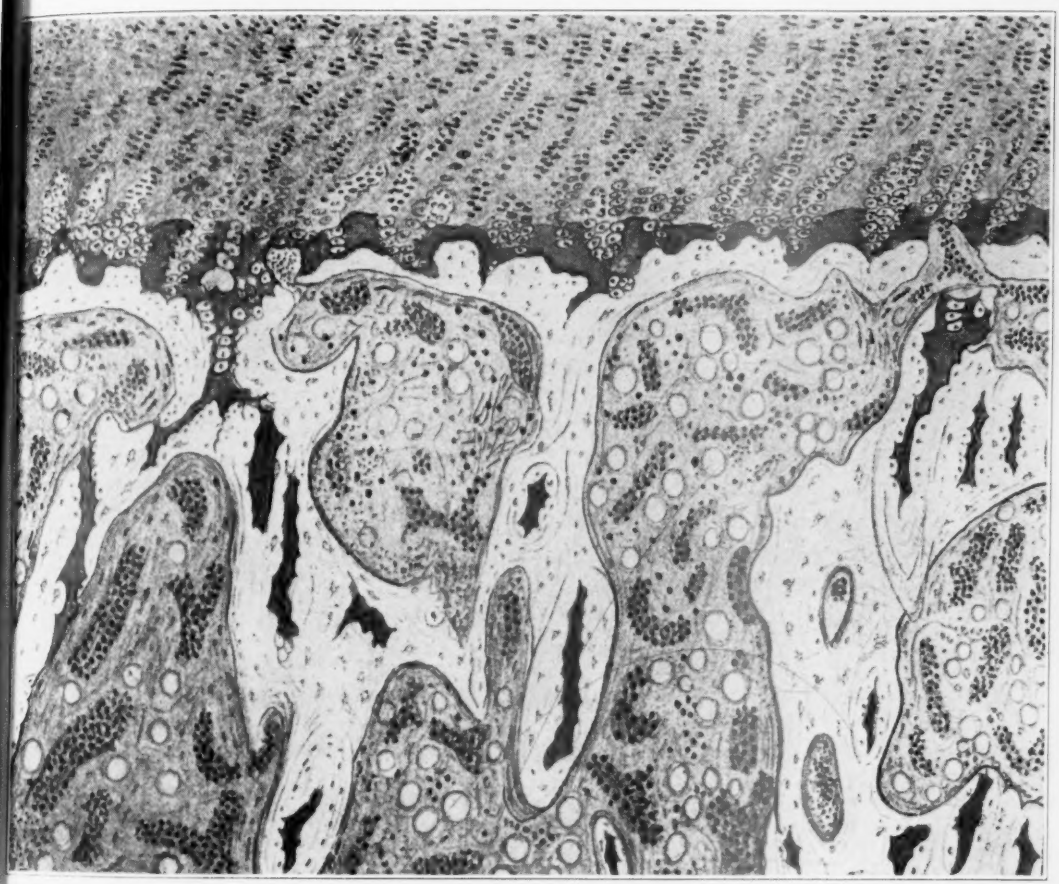

Fig. 12.—Section of bone, reproduced from Dieterle's article [14] describing a 4 month old cretin. The epiphysiodiaphysial junction consists of a layer of solidly calcified cartilaginous matrix (dark gray in the drawing) in apposition with a transverse layer of bone.

filamentous vascular projections of marrow there was present a solid disk of calcified cartilage in apposition with an almost equally solid disk of bone (fig. 12). The marrow was virtually excluded from this union.

More recently some attention has been directed to the study in cretins of pathologic processes occurring within the epiphysis. An observation

of some interest in this connection was reported by Lang,[15] who examined the hip of a male cretin of 10 years (figs. 13 and 14). Ossification of the capital epiphysis of the femur had not yet commenced, but the altered cartilage offered clear evidence of the perversion of orderly bony development. Although the articular surface was not affected, the interior of the epiphysis was observed to contain irregular areas of poorly stained tissue alternating with areas taking an intense basophilic stain. In places the cartilage had evidently disintegrated and had become replaced by cystic areas filled with dark-staining fluid. The deeply basophilic portions of the epiphysis, being well vascularized and containing hypertrophied cartilage cells, would appear to have been the seat of proliferative changes preparatory to ossification. One is there-

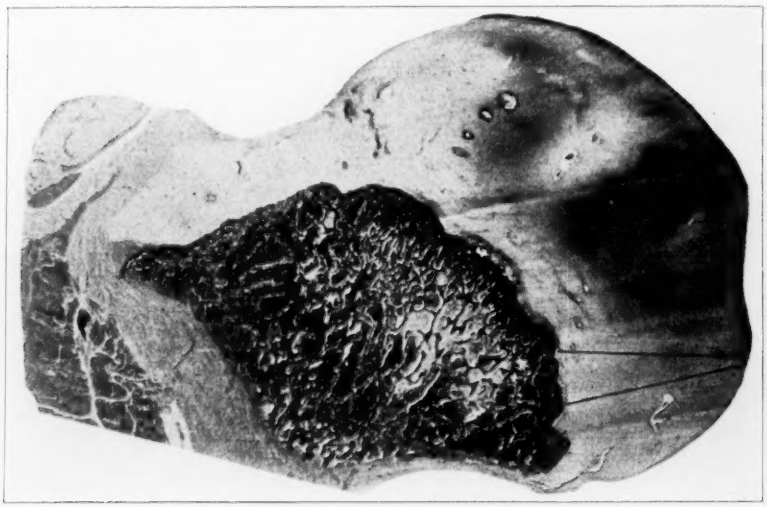

Fig. 13.—Section of a portion of the femur, reproduced from Lang's article [15] describing a 10 year old cretin. The irregular development of scattered foci of basophilic proliferative cartilage is readily apparent. Cystic degeneration may also be noted.

fore led to the conclusion that if the child had lived the capital epiphysis would have become ossified from multiple foci of relatively normal tissue separated from each other by areas of cartilage which had either failed to develop or had undergone cystic degeneration.

The interpretation which we have placed on the changes present in Lang's case is in accord with anatomic observations made by Looser [7] in a series of cretins. The latter investigator has commented on the fact

15. Lang, F. J.: Mikroskopische Befunde bei juveniler Arthritis deformans (Osteochondritis deformans juvenilis coxae Legg-Calvé-Perthes), nebst vergleichenden Untersuchungen über die Femurkopfepiphyse mit besonderer Berücksichtigung der Fovea, Virchows Arch. f. path. Anat. **239**:76, 1922.

that ossification of the head of the femur in cretinous persons does not proceed from a centrally located and concentrically enlarging zone of ossification. He observed rather that diffuse and irregular ossification of the capital epiphysis takes place with a more or less incomplete replacement of the cartilage by bone.[16] The process results in the persistence within the bony head of islands of cartilage, often large and roentgenographically discernible. These unossified rests, usually situated near the periphery, may be connected by cartilaginous extensions with the deeper zones of the head, where secondary degenerative processes

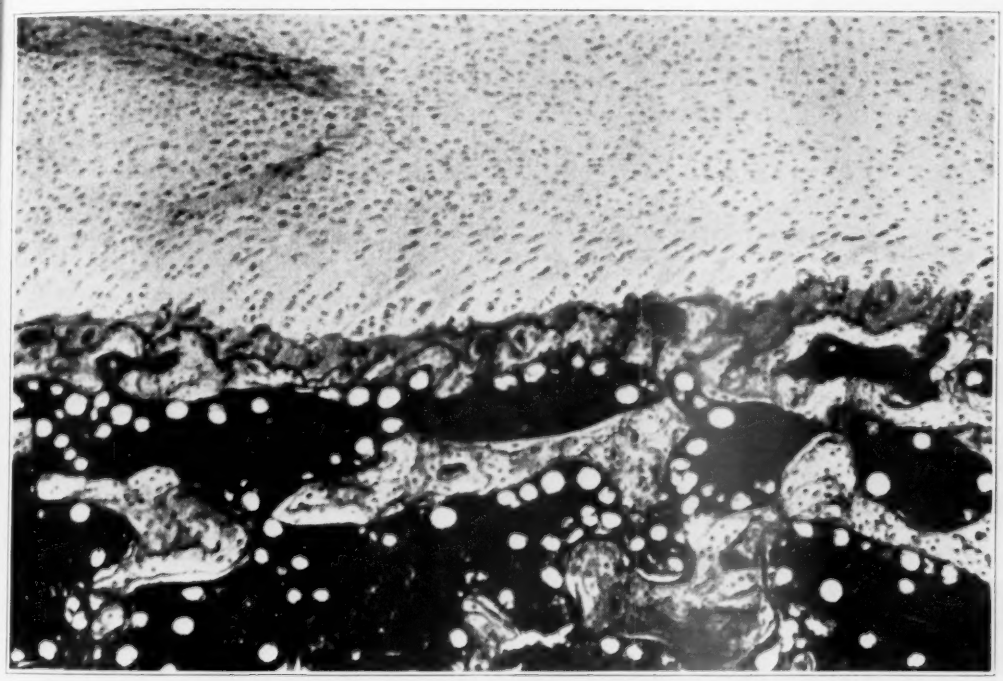

Fig. 14.—Higher magnification of the area between the two lines in figure 13, showing the pathologic nature of the junction of cartilage and bone. The calcified cartilaginous matrix in the photograph is dark gray, the marrow black.

are apt to supervene. Liquefaction of, and fibrotic changes in, the cartilage are responsible for the formation of fissures in the epiphysis, followed at times by actual fragmentation of portions of the head, with liberation of joint bodies. More frequently the diseased epiphysis,

16. Similar disturbances of ossification have been found by a number of observers to be present in many other epiphysial structures of cretins, but the head of the femur is the commonest site of involvement (Bircher,[2] plate 7, figure 66. Haumann, W.: Osteopathia cretinosa scapulae, Beitr. z. klin. Chir. **140**:136, 1927. Looser[7]).

unable to withstand the pressure of weight bearing and the repeated traumas of everyday life, becomes crushed and flattened.

Clinical Significance of Histologic Changes.—The bearing which these observations have in the elucidation of the clinical material presented here seems clear. The first of the pathologic processes described, involving the epiphysial plate, has significance for the interpretation of the condition in case 1, whereas the changes occurring within the epiphysis are of interest in the analysis of the condition in cases 2, 3 and 4. It has seemed reasonable to conclude in the one instance that an abnormal union of epiphysis and diaphysis of the type found in cretinism was an underlying factor in the pathogenesis of the slipped epiphysis. In the second group of cases the nature of the pathologic disturbance has served to clarify many of the roentgenographic features observed.

If one recalls the structural nature of the healthy epiphysial junction of cartilage and bone, the basis for the first conclusion becomes more apparent. Normally the epiphysis is firmly united to the shaft of the bone. Indeed, as the experiments of Rammstedt [17] indicate, it is almost impossible to effect a clean traumatic separation of the head of the femur from the neck, because the neighboring structures are weaker than the line of junction. This remarkable union of cartilage and bone is achieved by the interdigitation of fine processes of the calcified lattice with the opposing filamentous extensions of osteogenic marrow. It is as though the two were joined by a meshing of gear-teeth. Naturally, the interlocking character of the junction would fit it admirably to resist lateral stresses. It is entirely probable, however, that in case 1 the failure to take thyroid medication for a number of years had resulted in the formation of the "disk type" as opposed to the normal "mesh type" of union of bone and cartilage. As a consequence of this structural modification the femur was unable to withstand the shearing stress of the fall from a bicycle, and slipping of the epiphysis occurred.

It is necessary to point out that the disk type of configuration of the epiphysial plate seen in hypothyroidism corresponds to the alteration of bony structure occurring in other examples of delayed growth. It is this modification of pattern which results in the appearance of the roentgenographically visible transverse lines the nature of which has been elucidated by Harris and by Park and his collaborators.[18] The question which immediately arises as to whether periodic noncretinous arrests of growth, either affecting the entire skeleton or perhaps

17. Rammstedt, C.: Ueber traumatische Lösung der Femurkopfepiphyse und ihre Folgeerscheinungen, Arch. f. klin. Chir. **61**:559, 1900.

18. (*a*) Harris, H. A.: Bone Growth in Health and Disease, London, Oxford University Press, 1933. (*b*) Eliot, M. M.; Souther, S. P., and Park, E. A.: Transverse Lines in X-Ray Plates of the Long Bones of Children, Bull. Johns Hopkins Hosp. **41**:364, 1927.

restricted locally to the head of the femur, bear an etiologic relationship to slipped epiphysis is of course beyond the scope of this study. One is tempted nevertheless to speculate concerning the significance in the epiphysis of the widened transverse line seen in the preslipping stage in noncretins. Is it a growth line, and does it therefore indicate the presence also in these patients of the abnormal disk type of union between head and neck?

There remain to be discussed a few points in connection with cases 2, 3 and 4. It will be noted that many of the peculiarities exhibited in the roentgenograms of the children's hips find a ready explanation in the characteristic pathologic changes just described. The presence of large islands of cartilage persisting within the bony framework of the epiphyses is easily recognized, particularly in the lateral views. It has been our impression that the lateral views at times provide valuable information not obtainable from the more conventional anteroposterior angle. Thus, in case 2, the anteroposterior view of the left hip revealed a marked flattening of the epiphysis, which, but for the presence of many unossified areas, appeared to be otherwise intact. The lateral aspect of the hip, however, showed the presence of a deep central fissure with an appearance of beginning fragmentation. It will be recalled that this boy was the only one of the three of his group who suffered any pain in the hip, and it may well be that his symptoms were an indication of the extensive destruction suggested in the roentgenograms. The degree of flattening of the epiphyses, on the other hand, is perhaps better visualized in all the cases in the anteroposterior views. The presence in case 4 of a large scalloped-out portion of the superior margin of the head caused by the failure of ossification in that region is also well brought out in a roentgenogram taken from the latter angle.

While the roentgenograms in the three cases of osteochondrosis associated with hypothyroidism embody many of the features to be found in Legg-Calvé-Perthes' disease, it will be readily recognized that important differences serve to distinguish the two entities. It must of course be remembered that an anomalous development of the capital epiphysis has been considered by many to be the basic factor in the pathogenesis of the latter disease as well as in the syndrome under discussion here. Familial influences, the simultaneous presence of other congenital anomalies of the hip, and endocrine disorders, including even hypothyroidism,[19] have been variously cited as evidence favoring this hypothesis. Nevertheless it is an outstanding fact that Legg-Calvé-Perthes' disease affects hips known to have previously had normal roentgenographic architecture. Moreover, the evolution of the patho-

19. Cavanaugh, L. A.; Shelton, E. K., and Sutherland, R.: Metabolic Studies in Osteochondritis of the Capital Femoral Epiphysis, J. Bone & Joint Surg. **18:** 957 (Oct.) 1936.

logic processes occurring in the two diseases is distinctly different. The first pathologic change in osteochondritis deformans juvenilis is manifested by a diffuse increase in density of the epiphysis, apparently due to aseptic necrosis. Fragmentation, with production of detritic material, followed by early reparative processes in the form of invading fibrous granulation tissue, is responsible for the later appearance of areas of rarefaction in the roentgenograms. Subsequent regenerative processes akin to formation of callus occur in places, resulting in the development of islands of cartilage as well as areas of new bone. It is possible that in some cases such islands are produced also as a consequence of the breaking off and impaction within the epiphysis of portions of either the articular cartilage or the epiphysial plate.[20]

The osteochondrosis associated with hypothyroidism, by contrast, is a disease of the formative period of the epiphysis. Deposition of bone from the outset occurs in an irregular manner, appearing in multiple foci of ossification separated from each other by cartilage which has failed to undergo the necessary proliferative changes. It is obvious, therefore, that the islands of cartilage of the epiphysis in hypothyroidism have an entirely different origin from those found in Perthes' disease. It is only after the supervention of destructive and degenerative processes that the diseased epiphysis in hypothyroidism begins to resemble the pathologic picture present in osteochondritis deformans juvenilis.

SUMMARY AND CONCLUSIONS

In children suffering from deficient function of the thyroid gland a disturbance of ossification involving the capital epiphysis of the femur may occur. The maldevelopment is of two varieties. One of these affects the structure of the epiphysial plate in such a manner as to give rise occasionally to slipping of the epiphysis. The other is in the nature of osteochondrosis of the head of the femur. In either case deformities ensue which lead to the appearance of coxa vara.

On the basis of the osseous changes found in cretinism an explanation is offered to account for slipping of the epiphysis. What may be designated as a mesh type of union characterizes the junction of epiphysis and diaphysis in normal growing bones. A powerful interlocking of cartilage and bone is achieved by the interdigitation of the gear teeth of the calcified lattice with the opposing filamentous processes of bone-forming marrow. In cretins, however, the remarkably intimate association occurring at the normal epiphysial plate is replaced by a disk type of configuration in which a flat zone of solidly calcified cartilage is in apposition with a transverse layer of bone. It is pointed out that

20. Pich, G.: Histopathologic Study in a Case of Perthes' Disease of Traumatic Origin, Arch. Surg. **33**:609 (Oct.) 1936.

the disk type of union may be incapable of resisting stresses which are well borne by the normal mesh type. As a result the epiphysis in children with hypothyroidism may be dislodged. The possibility is mentioned parenthetically that the disk type of epiphysial plate may be a factor in the etiology of slipped epiphysis in children without hypothyroidism exposed to trauma during certain periods of their development.

The second type of lesion, osteochondrosis of the head of the femur, arises from an irregular bony development of the epiphysis, with the persistence of numerous islands of uncalcified cartilage. The roentgenographic features are discussed in relation to the pathologic changes which take place. The osteochondrosis is insidious in character and in the cases described here was discovered by means of roentgenograms. Subsequent examinations have led to the conclusion that it may be possible to detect the condition clinically. The finding in children with hypothyroidism of limitation of motion at the hip chiefly in internal rotation constitutes presumptive evidence of the presence of the disease of the hip.

Dr. J. P. Michelson gave us the opportunity of examining the patients with hypothyroidism under his care in the endocrine clinic.

NOTE.—Since this paper was submitted for publication an article describing the osteochondrosis of the femoral capital epiphysis due to cretinism has appeared (Reilly, W. A., and Smyth, F. S.: Cretinoid Epiphyseal Dysgenesis, J. Pediat. **11:** 786 [Dec.] 1937).

URINARY OUTPUT OF VITAMIN C OF NORMAL AND OF SICK CHILDREN

WITH A LABORATORY TEST FOR ITS ESTIMATION

THOMAS S. BUMBALO, M.D.
BUFFALO

Cevitamic acid (ascorbic acid, ascorbinic acid [German] or vitamin C) is one of the vitamins whose composition is known. In 1928 von Szent-Györgyi [1] isolated from plants and the cortex of animals adrenals a crystalline substance which he called hexuronic acid. Hexuronic acid was renamed ascorbic acid in 1933. At the present time the synthetic form of cevitamic acid, which takes its origin from dextrose, is clinically available and has been successfully used in the treatment of scurvy and allied conditions.[2]

Scientific interest in cevitamic acid has renewed interest in scurvy, a disease which, judging from clinical criteria, has come to be considered an interesting but rare clinical entity both in this country and in England.[3] While it is generally agreed that clinical scurvy is now rare, it is also agreed that various signs and symptoms associated with nutritional disorders in children and in some adults are related to scurvy and to vitamin C deficiency. Hence there is recognition of a clinically discernible syndrome variously described as subclinical scurvy, latent scurvy or vitamin C subnutrition.[4]

From the Department of Pediatrics of the Buffalo City Hospital and the University of Buffalo School of Medicine.

Submitted in partial fulfilment of the requirements for the degree of Master in the Medical Sciences, University of Buffalo.

1. von Szent-Györgyi, cited by Goettsch, E.: Treatment of Infantile Scurvy with Cevitamic Acid, Am. J. Dis. Child. **49**:1441-1448 (June) 1935.

2. Schultzer, P.: Treatment of Scurvy in Man with Intravenous Injection of Ascorbic Acid, Lancet **2**:589-590 (Sept. 9) 1933. Svensgaard, E.: Infantile Scurvy Treated with Ascorbic Acid, Lancet **1**:22-23 (Jan. 6) 1934. Bacharach, A. L.: Ascorbic Acid for Scurvy, ibid. **1**:427 (Feb. 24) 1934.

3. (*a*) Dalldorf, G.: A Sensitive Test for Subclinical Scurvy in Man, Am. J. Dis. Child. **46**: 794-802 (Oct.) 1933. (*b*) Wood, P.: A Case of Adult Scurvy, Lancet **2**:1405-1406 (Dec. 21) 1935. (*c*) Gilman, B. B., and Tanzer, R. C.: Subdural Hematoma in Infantile Scurvy, J. A. M. A. **99**: 989-991 (Sept. 17) 1932.

4. Hess, A. F.: Recent Advances in the Knowledge of Scurvy and the Antiscorbutic Vitamin, J. A. M. A. **98**:1429-1433 (April 23) 1932.

CLINICAL SYNDROMES

Scott,[5] of Philadelphia, recently reported a case of nontraumatic spontaneous subaponeurotic hematoma as one of subclinical scurvy. Aballí and Valledor [6] reported two cases of a condition practically identical to that in the case reported by Scott. Schroeder,[7] in describing subclinical scurvy, expressed the opinion that with a lack of vitamin C the coagulation time of the blood is prolonged and the number of platelets and of erythrocytes as well as the amount of hemoglobin is diminished before any symptoms of clinical scurvy are manifested. Widenbauer [8] named hemorrhagic diathesis as one of the many other possible forms of hypovitaminosis C. Gilman and Tanzer [3c] reported a case of subdural hematoma with vitamin C deficiency as the cause. Dr. Francis J. Gustina and I are submitting for publication from the files of the Buffalo City Hospital a similar case of subdural hematoma.

From the varying nature of cases reported it is clear that clinical syndromes resulting from vitamin C deficiency may be not only extremely unusual and interesting but also confusing. Therefore, an accurate and reliable laboratory procedure that can definitely determine the amount of vitamin C in body tissues and excretions and thus give an estimate of the vitamin C saturation or nutrition of the body is desirable. Such a procedure, besides being a laboratory test of scientific interest, lifts the aforementioned syndromes from the realm of questionable diagnoses and impressions to the realm of accurate clinical diagnoses substantiated by adequate laboratory proof.

While much work in the vitamin C determination of urine and of blood has been done in England and Germany, comparatively little has been done in this country. Reports on the estimation of cevitamic acid in blood are far fewer than reports on its estimation in urine, and the whole field has many possibilities and opportunities for original research.[9]

HARRIS-RAY METHOD OF DETERMINATION

In 1933 Harris and Ray introduced a chemical titration method for estimating the amount of cevitamic acid in urine. In 1935 and 1936 they reported sufficient data to prove that their technic can be used as

5. Scott, M.: Nontraumatic Spontaneous Subaponeurotic Hematoma: Its Probable Relation to Atypical Scurvy, J. A. M. A. **107**:348-350 (Aug. 1) 1936.

6. Aballí, A., and Valledor, T.: Dos casos atípicos de enfermedad de Barlow, Bol. Soc. cubana de pediat. **5**:201-212 (June-Dec.) 1933.

7. Schroeder, H.: Die Ausscheidung der Ascorbinsäure im gesunden und kranken Organismus, Klin. Wchnschr. **14**:484-487 (April 6) 1935.

8. Widenbauer, F.: Ascorbinsäurestudien an Klein- und Schulkindern, Jahrb. f. Kinderh. **146**:297-310 (May) 1936.

9. Taylor, F. H. L.; Faulkner, J. M., and Chase, D.: Estimation of Reduced Ascorbic Acid in Blood Serum and Plasma, Biochem. J. **30**:1119-1125 (July) 1936. Farmer, C. J., and Abt, A. F.: Determination of Reduced Ascorbic Acid in Small Amounts of Blood, Proc. Soc. Exper. Biol. & Med. **34**:146-150 (March) 1936.

an approved laboratory method for substantiating a diagnosis of hypovitaminosis C.[10] Subsequently their method was used by other English investigators[11] to determine the relation of vitamin C and vitamin C deficiency to rheumatic fever and to Addison's disease.

The titration technic described by Harris and Ray is a microchemical one. They recommended that the urine be titrated immediately after it is passed, or preserved with glacial acetic acid and titrated ten to twelve hours later. The principle of their titration is to take a measured amount of a recently standardized solution of the reducing dye 2,6-dichlorophenolindophenol (Tillmans' reagent) and determine the amount of urine which must be added to discharge its blue color. They used a 0.05 per cent solution of the dye, made acid by the addition of 2 drops of glacial acetic acid, so that 0.05 cc. of the dye was equivalent to roughly the amount of 0.025 mg. of cevitamic acid. They recommended two minutes or less for a single titration.

Using this microchemical method, which they called a titration method for the determination of the vitamin C content of urine "with considerable ease and accuracy," Harris and Ray observed that an infant suffering from scurvy excreted a smaller amount of vitamin C than a normal, well nourished child of the same age.[10a] They also observed that after cure the same infant excreted vitamin C at a full normal rate. To determine the state of vitamin C saturation or "unsaturation," they gave large test doses of vitamin C to the infant both during scurvy and after recovery. During scurvy repeated administration of large doses of vitamin C failed to bring about the urinary response characteristic of normal subjects. They explained that due to the state of vitamin C "unsaturation" practically all of the vitamin given to this infant was taken up by the tissues that were depleted of vitamin C, so that none appeared in the urine. However, after recovery, when the tissues were saturated with the vitamin, large amounts of it appeared in the urine. These authors made the same observation repeatedly in cases of scurvy.

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10. (*a*) Harris, L. J., and Ray, S. N.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, with a Note on Antiscorbutic Value of Human Milk, Lancet **1**:71-77 (Jan. 12) 1935. (*b*) Harris, L. J.; Ray, S. N.; Abbasy, M. A., and Marrack, J. R.: Diagnosis of Vitamin C Subnutrition by Urine Analysis, ibid. **2**: 1399-1405 (Dec. 21) 1935. (*c*) Harris, L. J.; Abbasy, M. A.; Yudkin, J., and Kelly, S.: Vitamins in Human Nutrition: Vitamin C Reserves of Subjects of the Voluntary Hospital Class, ibid. **1**:1488-1490 (June 27) 1936.

11. (*a*) Abbasy, M. A.; Hill, N. G., and Harris, L. J.: Vitamin C and Juvenile Rheumatism with Some Observations on the Vitamin C Reserves in Surgical Tuberculosis, Lancet **2**:1413-1417 (Dec. 12) 1936. (*b*) Archer, H. E., and Graham, G.: Some Observations on the Excretion of Ascorbic Acid, ibid. **1**: 710-713 (March 28) 1936.

The technic of Harris and Ray, while supported by other English workers, is by no means universally accepted.[12] The German workers support the methylene blue method of Martini and Bonsignore. With this method, they claim to detect the highest percentages of cevitamic acid in solution of the acid of known concentrations. Some of them were unable to arrive at the conclusions of Harris and Ray. Ammon and Hinsberg [13] in their work concluded that urine contains other reducing substances, such as cysteine and glutathione, which appreciably disturb the reaction. Harris and Ray, on the other hand, claimed that if the titration is carried out rapidly these possible interfering agents will not oxidize the indicator.

MODIFICATION OF HARRIS-RAY METHOD

In October 1936 attempts to duplicate the results of Harris and Ray were made in the laboratories of the Buffalo City Hospital with ultimate success. At first their technic was followed exactly, but the results obtained varied considerably from one titration to another. It was then decided to modify Harris and Ray's method. Since most microchemical procedures are subject to some inaccuracies because of the small quantities used, and since the Harris and Ray method calls for a final volume of less than 0.5 cc. following the titration, a macrochemical titration method which offered greater possibilties for accuracy was evolved. That method, used throughout this study, is as follows:

From 2 to 15 cc. of urine is brought to a final volume of 15 cc. and then brought to a p_H of 4.7 by the addition of 0.02 cc. of glacial acetic acid, congo red being used as an indicator. It is then titrated with Tillman's reagent to an end point at which a lilac blue color persists for at least fifteen seconds. Tillman's reagent is prepared so that 20 mg. of the dye is contained in 100 cc. of the dye solution. It is then standardized against a standard solution of cevitamic acid. Since it has been determined that 1 mg. of cevitamic acid is the equivalent of 2.116 mg. of Tillman's reagent, results may be easily calculated in terms of the amount of cevitamic acid excreted in twenty-four hours.

When this method was used, the results obtained checked consistently. The method is simple and offers little difficulty. A p_H of 4.7 appears to be the optimum for recovering the highest percentage of cevitamic acid, a higher p_H definitely lowering percentage of recovery, while a lower p_H influences results less obviously. Care must be taken to use fresh solutions of Tillman's reagent, as the solution deteriorates from day to day. With this comparatively simple technic, as high as 98 per cent of the cevitamic acid has been recovered from aqueous solutions of the acid of known concentration.

12. Wilkinson, J. F., and Ashford, C. A.: Vitamin C Deficiency in Addison's Disease, Lancet **2**:967-970 (Oct. 24) 1936.

13. Ammon, R., and Hinsberg, K.: Bemerkungen zu den Vitamin C-Bestimmungsverfahren im Urin, Klin. Wchnschr. **15**:85-88 (Jan. 18) 1936.

COMMENT

In the course of experimentation with this modification of the Harris and Ray technic, my associates and I tested a number of substances to determine whether they interfere with the titration. We found that phenols, uric acid, aminoacetic acid, urea, creatinine, acetone, lactic acid and dextrose do not oxidize 2,6-dichlorophenolindophenol, the indicator used in this study.

I am of the belief that this modification of the Harris and Ray technic is sufficiently accurate and easy to be of definite aid in substantiating a diagnosis of vitamin C subnutrition and in ruling out indefinite syndromes that may be confused with subclinical scurvy. This laboratory procedure is not offered as a means to diagnose clinical scurvy, because real clinical scurvy, while a rare disease entity, is easy to diagnose and requires no laboratory procedure for its identification.

TABLE 1.—*Normal Group* *

Case	Age	Sex	Nutrition	Urine Output per 24 Hours, Cc.	Vitamin C Output per 24 Hours, Mg.
B. M.	5	F	Very good	875	71.2
J. B.	13	M	Good	910	11.2
P. M.	5	M	Obese	870	36.8
T. B.	12	M	Very good	1,000	15.0
T. B.	12	M	Very good	1,000	20.6
F. S.	6	M	Very good	1,000	22.5
W. J.	10	M	Very good	1,000	37.6
S. J.	11	M	Very good	900	22.5
V. D.	9	M	Very good	860	22.0
E. C.	11	F	Very good	960	31.9
J. C.	10	F	Very good	1,000	29.5
M. C.	9	F	Very good	800	24.4
R. B.	8	M	Very good	900	23.5
J. B.	6	M	Obese	840	25.6
B. C.	10	M	Very good	860	26.2
J. G.	9	M	Poor	670	21.0

16 cases; average, 27.59 mg.

* All children in this group were white.

NORM FOR MINIMAL URINARY OUTPUT

Harris, Hill and Abbasy in their more recent work [11a] have established a normal minimal urinary output of vitamin C for a period of twenty-four hours for adults. They have shown that with a minimum optimal intake of vitamin C the average daily urinary excretion of cevitamic acid averages 13 mg. In an attempt to set up a similar normal standard for children, I studied the urine of a group of normal children who lived in average "middle class" American homes and on the normal diet of this class. Most of the children were of school age, and their activities were those of the average school child.

Table 1 shows the great variance in the urinary output of vitamin C of these children per twenty-four hours. The highest excretion, that

of a normal 5 year old girl, whose diet included from four to five large oranges daily, was 71.2 mg. The lowest excretion, that of a normal 13 year old boy, whose daily diet included a glass (about 60 cc.) of orange juice with his breakfast, was 11.2 mg. The average output for this group of sixteen normal children was 27.59 mg. It is difficult to establish any fixed figure as the normal excretion of vitamin C for a period of twenty-four hours, but an output of 10 mg. or over certainly falls within the minimal limit for this group of normal children. Their

TABLE 2.—*Tuberculous Group*

Case	Age	Color	Sex	Physical State	Nutrition	Urine Output per 24 Hours, Cc.	Vitamin C Output per 24 Hours, Mg.
L. B.	13	White	F	Pulmonary tuberculosis with cavitation	Good	2,260	10.3
J. B.	9	Colored	M	Childhood tuberculosis and pleurisy with effusion	Fair	800	3.0
U. F.	7	Colored	M	Pulmonary tuberculosis with cavitation	Fair	800	4.5
F. E.	13	Colored	M	Chronic pulmonary tuberculosis with cavitation	Poor	1,060	8.7
T. C.	14	White	F	Pulmonary tuberculosis and peritonitis	Good	700	4.6
K. C.	13	White	F	Tuberculous adenitis	Very good	1,000	10.5
R. M.	14	White	F	Pulmonary tuberculosis with beginning cavitation	Poor	1,100	6.8
R. M.	14	White	F	Pulmonary tuberculosis with beginning cavitation	Poor	950	7.1
R. R.	11	White	M	Tuberculous spine	Fair	1,000	5.6
J. Y.	11	White	M	Tuberculous spine with positive sputum	Fair	900	5.9
B. G.	9	White	F	Childhood tuberculosis	Fair	1,000	7.5
J. C.	10	Colored	M	Childhood tuberculosis	Poor	700	21.3
L. B.	13	White	F	Pulmonary tuberculosis with cavitation	Fair	1,130	7.6
S. M.	8	White	M	Tuberculosis of left hip	Poor	1,100	9.4
V. F.	5	White	F	Pulmonary tuberculosis	Good	600	3.9
M. B.	6	White	F	Pulmonary tuberculosis	Fair	600	9.0

16 cases; average, 7.8 mg.

excretions are by far greater than the Harris-Ray "normal value of about 1 to 2 mg. for a young child . . . on an average 'middle class' or 'higher working class' diet." [10a]

AVERAGE OUTPUT FOR SICK CHILDREN

Table 2 shows the twenty-four hour urinary excretion of a group of sick children who were selected from the tuberculosis service of the Buffalo City Hospital. All sixteen members of this group, both bed and ambulatory patients, had active tuberculosis. Their diet, the average hospital fare supplemented with extra foods given for extra nourishment, had an approximate daily vitamin C value of from 50 to 60 mg.

The highest excretion for this group was 21.3 mg., excreted by a 10 year old Negro girl of poor nutrition whose diet included extra fruit brought in by her relatives. The lowest excretion of the group was 3 mg., excreted by a Negro boy 9 years of age with childhood tuberculosis and pleurisy. The average output for this group was 7.8 mg., a figure far below 11.2 mg., the lowest value for the normal class. While 16 cases are not enough to permit definite conclusions, the consistently low figures do suggest some vitamin C deficiency in tuberculosis. Similar conclusions have been arrived at by both English and German workers.[14]

TABLE 3.—*Sick Group (Exclusive of Tuberculous Patients)*

Case	Age	Color	Sex	Physical State	Nutrition	Urine Output per 24 Hours, Cc.	Vitamin C Output per 24 Hours, Mg.
M. G.	5	White	F	Fracture of left tibia	Fair	600	16.9
R. C.	6	White	F	Acute rheumatic fever	Poor	300	13.8
R. C.	6	White	M	Acute rheumatic fever	Poor	430*	10.0
R. C.	6	White	M	Acute rheumatic fever	Poor	500*	7.9
M. D.	8	Colored	M	Recent right upper lobe pneumonia	Poor	700	9.1
D. B.	12	White	M	Ruptured appendix with peritonitis	Poor	500	6.5
W. B.	12	White	M	Osteomyelitis	Fair	1,800	15.5
A. R.	6	White	F	Second degree burn of left leg	Fair	600	3.9
C. H.	12	Colored	F	Potts fracture of left leg	Good	800	5.2
J. G.	7	White	M	Chronic otitis media	Fair	650	11.7
B. B.	5	Colored	F	Acute bronchitis	Fair	550	4.1
E. S.	7	White	M	Acute otitis media	Fair	500	3.9
A. A.	12	Colored	F	Acute appendicitis	Good	600	3.8
J. B.	9	White	M	Pneumonia	Poor	1,000	6.0
J. B.	9	White	M	Pneumonia	Poor	1,000*	7.5
N. B.	4	White	F	Empyema and measles	Poor	450	3.5
R. C.	5	White	M	Acute gastrointestinal upset	Poor	550	8.7
W. L.	12	White	M	Fracture of left tibia	Fair	800	6.8
G. G.	13	White	F	Arthritis	Fair	850	7.1
V. G.	13	White	F	Dermatitis venenata	Fair	600	5.6
S. M.	8	White	M	Undetermined lesion of hip	Poor	800	6.1

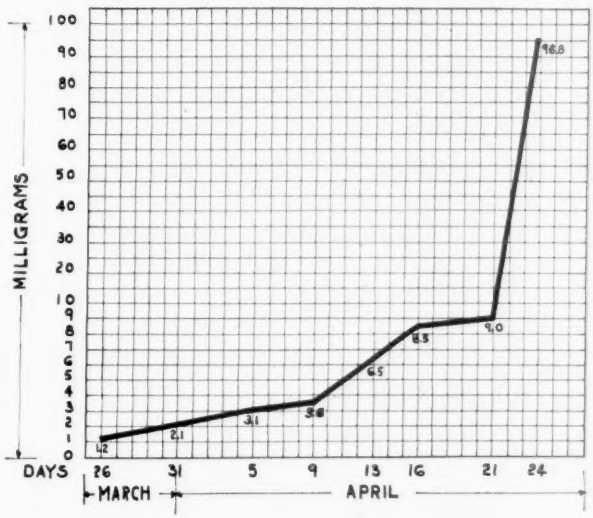
21 cases; average, 7.8 mg.

Table 3 shows the twenty-four hour urinary excretion of vitamin C of a group of sick children from the pediatric and surgical services of the Buffalo City Hospital. Of these 18 children, 2 were of good nutrition, 9 of fair nutrition and 7 of poor nutrition. The diet of this group did not include extra foods given between meals. Two children of the group, R. C. and J. B., were followed over a period of three and of two weeks, respectively, with determinations of the vitamin C in the urine at six day intervals. The first child, who had acute rheumatic fever, showed a moderate decrease in his vitamin C output, from 13.8 mg. to 10 mg. to 7.9 mg. The second child who had pneumonia,

14. Hasselbach, F.: Das Vitamin C-Defizit bei Tuberkulösen, Deutsche med. Wchnschr. **62**:924-928 (June 5) 1936. Footnote 11.

showed a moderate increase, from 6 mg. to 7.5 mg. This increase was noted as the child improved clinically. For this group the average output was 7.8 mg. lower than the average for the normal group. The consistently low figures for the third group suggest some vitamin C deficiency in febrile conditions. Wilkinson and Ashford [12] also have observed that many hospital patients show vitamin C deficiency.

Most of the children in the group came from very poor families on the city relief rolls, and their unsatisfactory nutritional state points unmistakably to generally deficient home diets. This factor naturally influences the vitamin C element in their nutrition. Undoubtedly there are among this group, as shown by the low urinary output of vitamin C



Urinary output of vitamin C in a case of scurvy (D. K.).

per twenty-four hours, children with cases of latent scurvy which present no definitely discernible clinical symptoms or perhaps only vague symptoms that are shadowed by the picture of whatever principal medical or surgical lesion prompted hospitalization. Further, perhaps some of the signs and symptoms included as part of the clinical picture of a specific disease entity are really signs and symptoms of subclinical scurvy.

REPORT OF A CASE

The chart following table 3 illustrates the urinary output of vitamin C in a case of known mild scurvy. D. K., a poorly nourished white girl, 4 years of age (data for whom are not included in the preceding tables), was admitted to the Buffalo City Hospital on March 19, 1937, with a diagnosis of ulcerative tonsillitis and otitis media on the left side with early involvement of the mastoid. In addition to the acute tonsillitis and otitis media, this child presented swollen gums that

bled easily. The gum picture was not typical of scurvy but did suggest some vitamin C deficiency. A week after her admission, studies of the urine showed a low vitamin C output, which substantiated a clinical diagnosis of scurvy. Beginning March 30, 50 mg. of cevitamic acid was administered daily. Long after her gums became healthy, low urinary excretion of vitamin C persisted, but on April 23, the output abruptly rose to 96.8 mg. By this time she had received 1,250 mg. of cevitamic acid orally, not including the vitamin C taken in her food. The child remained in the hospital forty-six days and, after a mastoidectomy, was subsequently discharged as completely recovered.

This peculiar response to cevitamic acid taken in large doses is characteristic of scurvy.[10] The urinary output remains low until the tissues depleted of vitamin C become saturated, when the excess of the vitamin is excreted in the urine.

SUMMARY

A macrochemical modification, both easy and accurate, of the Harris and Ray method for the determination of cevitamic acid is presented.

The urinary excretion of cevitamic acid of a normal child on an average diet is found to range from 11.2 to 71.2 mg. per twenty-four hours, directly dependent on the vitamin C intake.

The results of the study suggest that there is some vitamin C deficiency in all forms of tuberculosis in children. It is suggested also that there is some vitamin C deficiency in all febrile conditions in children.

A case of scurvy in a child 4 years of age, with cevitamic acid treatment and complete recovery, is presented. The urinary vitamin C output in a case of scurvy is seen to remain low even when large oral doses of cevitamic acid are given. The urinary vitamin C output is seen to rise abruptly and to a high level when the tissues of the patient have become saturated with the vitamin. This may take some days and may not occur until days after the signs and symptoms of scurvy have disappeared.

Dr. Walter W. Jetter assisted in the chemical studies.

333 Linwood Avenue.

ONE HOUR, TWO DOSE DEXTROSE TOLERANCE TEST

MOSES COOPERSTOCK, M.D.

AND

JOSEPHINE M. GALLOWAY, B.S.

MARQUETTE, MICH.

Several years ago, Exton and Rose [1] published their results with the use of a one hour, two dose alimentary dextrose tolerance test for adult subjects; they claimed for it, in addition to the important factor of time saving, greater specificity and reliability than are found in the older tests. Kelly, Beardwood and Fowler [2] confirmed the usefulness of this new procedure. Gould, Altshuler and Mellen,[3] in comparative studies, likewise corroborated the advantages of this shorter test, finding, however, a necessity for modification of both the technic and the diagnostic criteria. It seems apparent that if applicable with equal success to infants and children, such a test would be especially advantageous for them and should find ready advocation for its use.

This newer test is based on the paradoxic law, long ago expressed by Allen,[4] that ". . . whereas in normal individuals the more sugar given the more is utilized, the reverse is true in diabetes." It has since been abundantly demonstrated that when normal human beings are given repeated doses of dextrose, the insulin-glycogen mechanism so operates that either hypoglycemia or little or no change in the blood sugar level is produced, in contrast to the failure of this mechanism in diabetes, in which hyperglycemia results from repeated administration of dextrose.

Well aware of the diagnostic limitations of the conventional oral sugar tolerance tests, Exton and Rose [5] had previously investigated the

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From the Northern Michigan Children's Clinic and St. Luke's Hospital.

1. Exton, W. G., and Rose, A. R.: The One-Hour Two-Dose Dextrose Tolerance Test, Am. J. Clin. Path. **4**:381, 1934.

2. Kelly, H. T.; Beardwood, J. T., and Fowler, K.: The Value of the One-Hour Two-Dose Glucose Tolerance Test (Exton and Rose) in the Early Diagnosis of Diabetes Mellitus, Am. J. Clin. Path. **5**:411, 1935.

3. Gould, S. E.; Altshuler, S. S., and Mellen, H. S.: The One-Hour Two-Dose Glucose Tolerance Test in the Diagnosis of Diabetes Mellitus, Am. J. M. Sc. **193**:611, 1937.

4. Allen, F. M.: Studies Concerning Glycosuria and Diabetes, Boston, W. M. Leonard, 1913.

5. Exton, W. G., and Rose, A. R.: Diabetes as a Life Insurance Selection Problem, Proc. A. Life Insur. M. Dir. America **18**:252, 1931.

factors which affect their specificity. The factors which they found to be of chief importance in this connection are: the time taken to perform the test, antecedent dietary habits and the rate of absorption of ingested dextrose from the intestine.

They found that with the older method as definite information was obtainable at the end of two hours as after three or four hours. In studying the relation of dietary factors from a practical angle, these authors tested a number of subjects under the conditions of their daily food habits, in order to conform with customary practice, and found that antecedent diets do not affect the results of the new procedure. This was in contrast to the findings of Sweeney,[6] who demonstrated that the blood sugar curves obtained with the older method can be altered by different antecedent diets.

The factor that shows the most irregular behavior is the rate of absorption of dextrose from the intestinal tract. Certain experimental evidence in the literature[7] indicates that concentrations of dextrose ranging from 10 to 20 per cent disappear most rapidly from the stomach. Exton and Rose chose a 15 per cent concentration of dextrose, which they believed to be physiologically most suitable for their test.

In their procedure, Exton and Rose administer to their adult subjects 100 Gm. of dextrose in 650 cc. of water, divided into two equal doses. The test is performed usually after an overnight fast. Samples of blood and urine are collected prior to administration of the first dose of dextrose. One or two minutes is allowed for ingestion of the dextrose solution. Thirty minutes later, a second sample of blood is collected and the remaining dose of dextrose is given, one or two minutes again being allowed for its ingestion. Thirty minutes after ingestion of the second dose of dextrose samples of blood and urine are collected for the third and last time.

Gould, Altshuler and Mellen[3] used a 40 instead of a 15 per cent solution, having found in comparative tests that identical curves were obtained with these solutions. Ingestion of the large volume of liquid necessitated by the weaker solution, they claimed, was objectionable to their patients.

For the past two years we have employed the one hour, two dose dextrose tolerance test, modified to suit infants and children. A total of 102 tests were performed on 82 subjects. Of the group tested, 16 were patients with diabetes mellitus of varying duration and degree:

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6. Sweeney, J. S.: Dietary Factors That Influence the Dextrose Tolerance Test, Arch. Int. Med. **40**:818 (Dec.) 1927.

7. Beeler, C.; Bryan, A. W.; Cathcart, E. P., and Fitz, R.: An Improved Alimentary Glucose Tolerance Test, J. Metabolic Research **1**:549, 1922. Magers, E. J.: A Comparison of Blood Sugar Curves When Glucose Is Given Orally and Intraduodenally, J. Lab. & Clin. Med. **19**:608, 1934.

30 were normal subjects or patients in good nutritional status with conditions not known to be associated with any disturbance of carbohydrate metabolism, these serving as a control group, and 36 were patients with a variety of nondiabetic conditions.

PROCEDURE

In adapting the one hour, two dose dextrose tolerance test to infants and children, the response to variations in the dose and the concentration of dextrose to be administered was studied before a standard method was adopted. Because of the great range in size and weight of subjects in this group, it appears better to determine the dose of dextrose on the basis of body weight than to use a fixed dose, as in the test originally employed for adults. An exception was made in the case of infants weighing less than 7 Kg., for whom a minimum total dose of 10 Gm. of dextrose was employed. Similarly, MacLean and Sullivan,[8] in performing the older dextrose tolerance test, used not less than 10 Gm. for infants. For the majority of the subjects weighing above 7 Kg. between 1.5 and 1.75 Gm. of dextrose per kilogram of body weight was the dose used, the latter dose being the one now regularly employed. The concentration of dextrose was between 15 and 20 per cent, the more concentrated solution being given to older children for whom a larger amount of diluent was necessary. The test was performed after an overnight fast in the case of children who were receiving three meals daily. In the case of infants given a formula by schedule, the early morning feeding was omitted prior to the test.

Blood sugar values were obtained simultaneously by venous and by capillary samples for 11 patients to determine whether the micromethod was sufficiently reliable to warrant its routine use, which would further simplify the procedure. Good correlation between the venous and the capillary blood values was obtained. Subsequently the micromethod was employed except for premature and very young infants, from whom it was difficult to obtain even 0.1 cc. of blood by puncture of the skin. MacLean and Sullivan[8] reported similar difficulties with use of the micromethod for infants. The sugar values of venous and capillary blood were determined by the methods of Folin and Wu.

COMMENT

Exton and Rose established the following criteria of normal responses to the one hour, two dose test: 1. Values of blood taken after fasting are within the normal limits of the particular method employed. 2. The rise in the blood sugar level does not exceed 75 mg. in the thirty minute sample. 3. The amount of blood sugar in the sixty minute sample is less or the same or does not exceed that in the thirty minute sample by more than 5 mg. 4. All samples of urine give negative reactions to Benedict's test.

The types of normal response of the blood sugar to the one hour, two dose dextrose tolerance test are illustrated in chart 1. The chief difference between the blood sugar curve obtained by the new proce-

8. MacLean, A. B., and Sullivan, R. C.: Dextrose Tolerance in Infants and in Young Children, Am. J. Dis. Child. **37**:1146 (June) 1929.

dure as compared with that of the single dose method lies in the response to the second administration of dextrose. The first part of the curve does not differ essentially from that of the older method. The blood sugar level after the second ingestion of dextrose has a tendency to show a more or less abrupt fall, as illustrated in the curves of C.S. and T.C. Occasionally, as in the case of T.C., the final blood sugar value may fall considerably below that of a specimen taken during fasting. This phenomenon is also observed normally with the older, single dose method. The type of curve in which a fall occurs in the second part represents the typical response of the majority of subjects with normal carbohydrate metabolism. The type of curve in which there is a rise in the sixty minute blood sugar determination (F.V.) occurs with considerably less frequency.

Thirty-four tests were performed for 30 controls, whose ages varied from 1 month to 14 years. The average level of sugar in specimens of blood taken after fasting was 91 mg. per hundred cubic centimeters. The average for the thirty minute tests was 121 mg. The increase in the thirty minute value ranged from 10 to 62.8 mg., with an average of 29.2 mg. At sixty minutes the value of the blood sugar fell below the thirty minute level in 26 instances (76.5 per cent). The sixty minute level exceeded the thirty minute level in 8 instances (23.5 per cent), varying from 5 to 35 mg. above it (5, 8, 9, 13, 13, 14, 20 and 35 mg., respectively). While the sixty minute exceeded the thirty minute determination by over 5 mg. in 7 instances, in no case did the total rise exceed by 80 mg. the normal value of specimens taken during fasting.

Ten of this group of control subjects were between the ages of 1 month and 2 years. The only significant difference between the blood sugar values of these subjects as compared with values of those over 2 years of age was a smaller average rise at thirty minutes (22 mg. as compared with 32 mg.), probably indicating a greater tolerance for dextrose in the younger subjects.

In 49 tests performed for 41 patients with nondiabetic conditions, a total rise of more than 80 mg. above the normal blood sugar level occurred in only one instance (L.G., chart 2). It is interesting to note in this case that whereas the curve obtained by the one hour, two dose method is of the characteristic diabetic form, the curve obtained with the single dose method has an opposite, hypoglycemic tendency. It is noteworthy that glycosuria appeared in the one hour specimen with both tests: With the two dose method the blood sugar level was 235 mg. at one hour, and with the single dose method, 133 mg. It is probable that a much higher blood sugar value would have been found had a thirty minute determination of the blood sugar level been made in the single dose test. It is of further interest to observe that the two and three hour blood sugar values with the single dose method were at a hypo-

glycemic level and that the child had convulsions at a time when the blood sugar level was 62 mg. It is doubtful, however, that this seizure was of true hypoglycemic origin, since during convulsions induced by McQuarrie's [9] water-forcing, antidiuresis test for epilepsy the child's blood sugar level was normal. The variability of response to oral dextrose tolerance tests in epilepsy has been demonstrated, glycosuria occurring in 20 per cent of the patients.[10]

The limit of 5 mg. set by Exton and Rose as the allowable normal increase at sixty minutes seems, from an analysis of both the control

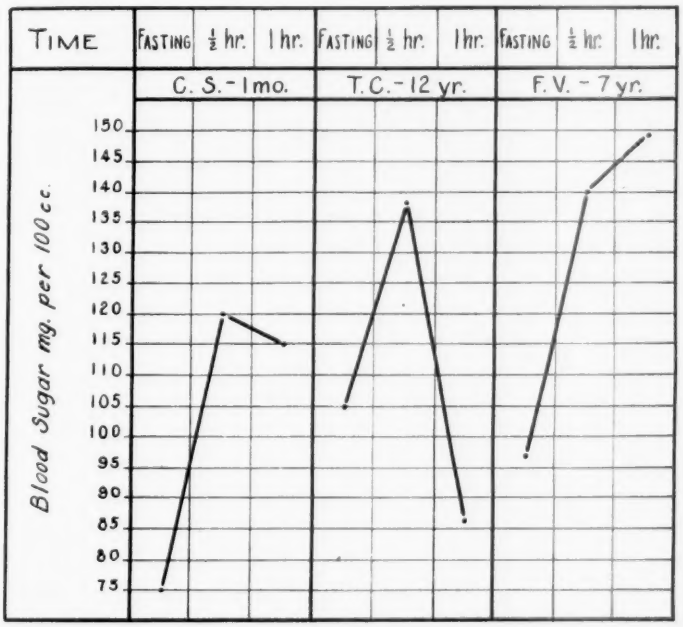

Chart 1.—Three types of normal blood sugar curves obtained by the one hour, two dose dextrose tolerance test. The curve of C.S. shows a slight fall in the second part, while that of T.C. shows a sharp fall, the blood sugar reaching a level below that of the value during fasting. The curve of F.V. shows a slight elevation in the second part. The first part of all three curves is similar to that obtained with the standard, single dose dextrose tolerance test, i. e., there is a more or less abrupt rise.

and the nondiabetic group, to be far too low. Gould and others [3] found that in 59 of 158 (37 per cent) of their nondiabetic patients (including,

9. McQuarrie, I., and Peller, D. B.: Effects of Sustained Pituitary Antidiuresis and Forced Water Drinking in Epileptic Children, J. Clin. Investigation **10**:915, 1931.

10. Pollock, L. J., and Boshes, B.: Carbohydrate Metabolism in Epilepsy, Arch. Int. Med. **59**:1000 (June) 1937.

however, 30 arteriosclerotic subjects) the blood sugar level rose at least 10 mg. above the thirty minute level. From the point of view of permissible technical variation alone, this limit of 5 mg. appears untenable. That the total rise above the normal level of specimens taken during fasting is the most important criterion is substantiated by the fact that only one discrepancy occurred in 83 tests performed on controls and on patients with nondiabetic conditions.

In the new test for diagnosis of diabetes the blood sugar curve, as described by Exton and Rose, is characterized chiefly by a more or less steep rise of not less than 10 mg. in the second part, the sugar values for

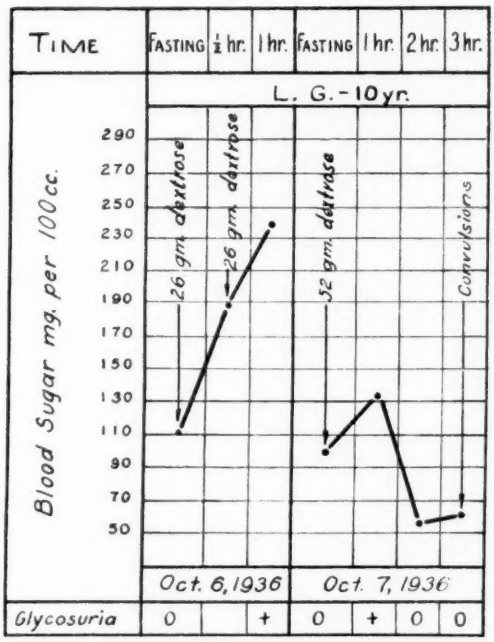

Chart 2.—Atypical result with the one hour, two dose dextrose tolerance test. L.G. had epileptiform seizures once or twice every three months. The diagnosis of epilepsy was confirmed by McQuarrie's water-forcing, antidiuresis test. A diabetic type of curve was produced with the one hour, two dose test. The opposite trend appears in the curve with the conventional, single dose test. Convulsions occurring when the blood sugar level was 62 mg. were probably not of hypoglycemic origin, since a blood sugar determination obtained during a subsequent episode of convulsions was normal.

the blood and urine standing in quantitative relation to the severity of the disease. For renal glycosuria the criteria submitted are blood sugar values which follow the normal course or which in any event never reach the diabetic level, and sugar in both specimens of urine. In cases of alimentary glycosuria, the specimen of urine taken during fasting is

free from sugar, although sugar appears in the final specimen. The blood sugar values follow the normal curve, even when the level is higher than normal.

The use of an alimentary dextrose tolerance test in the diagnosis of diabetes mellitus is primarily indicated when the blood sugar value for specimens taken in the morning during fasting is within normal range, a tendency that is present in early stages of diabetes in children. Illustrated in chart 3 are several types of blood sugar response to the one hour, two dose dextrose tolerance test in early stages of untreated

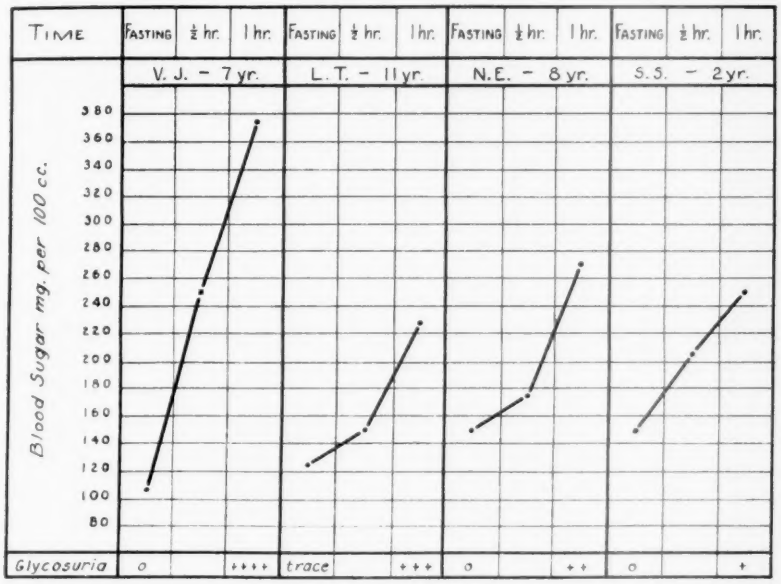

Chart 3.—Types of diabetic blood sugar curves in cases of early untreated juvenile diabetes obtained with the one hour, two dose dextrose tolerance test. For V. J. the blood sugar level during fasting is within normal limits; there is a sharp rise in the thirty minute sample and a continued steep rise at one hour. (The dose of dextrose was 2.8 Gm. per kilogram of body weight in a 16.5 per cent solution. The dose employed for all other patients illustrated was from 1.5 to 1.75 Gm. per kilogram of body weight in a solution of from 15 to 20 per cent.) Sugar was absent from the specimen of urine taken during fasting; it was present (4 plus) in the sixty minute specimen. L.T. during fasting had a blood sugar level slightly above normal, with a trace of sugar in the simultaneously taken specimen of urine. A slow rise appears in the first part of the curve and a sharp rise in the second part. There was glycosuria (3 plus) on the final examination. There was a low renal threshold for sugar. N.E. during fasting had a blood sugar level moderately above normal, with aglycosuria. A slow elevation appears in the thirty minute specimen, but a steep rise in the sixty minute specimen. Sugar (3 plus) was noted in the final specimen of urine. S.S. while fasting had a blood sugar level moderately above normal, with aglycosuria. A steep rise is seen in both the thirty and the sixty minute specimen. Glycosuria (1 plus) appeared in the sixty minute specimen.

juvenile diabetes. V.J. had a blood sugar value within normal limits during fasting, but there was a steep rise in the thirty and sixty minute determinations. (In this instance the dose of dextrose was 2.8 Gm. per kilogram of body weight.) L.T. showed only a moderate increase in the value of the thirty minute sample above the 124 mg. value for a specimen taken during fasting, but a distinctly sharp rise in the blood sugar level occurred at one hour. A trace of glycosuria in the specimen taken during fasting was associated with a blood sugar level slightly above normal, indicating a low renal threshold for sugar. N.E. and S.S. during fasting showed blood sugar levels above normal but below their renal thresholds for sugar. N.E. exhibited a slow rise in the

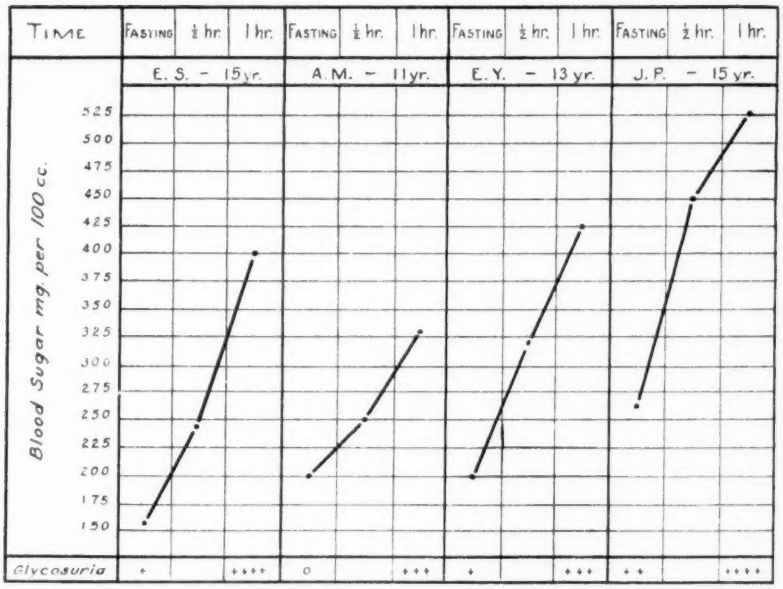

Chart 4.—Results of the one hour, two dose dextrose tolerance test for children with diabetic conditions of varying duration and severity. All patients received 175 Gm. of carbohydrate and between 1,990 and 2,120 calories. E.S. had a diabetic involvement of five years' standing, controlled by 58 units of regular insulin. A.M. had diabetes of six months' duration, controlled by 15 units of regular insulin. E.Y. had diabetes of one year's duration, controlled by 28 units of regular insulin. These patients under practically the same degree of control exhibited variations in their dextrose tolerance curves. J.P. had a poorly controlled diabetic condition of twenty months' duration; 50 units of regular insulin were given daily.

thirty minute blood sugar value, whereas S.S. showed a steeper elevation.

In modifying the criteria for diagnosis of diabetes by the one hour, two dose dextrose tolerance test, Gould and others [3] stated that the

condition may be correctly diagnosed if at least two of the following three conditions are encountered: (1) a blood sugar value during fasting which exceeds 120 mg.; (2) a level in the half-hour test which exceeds the level for specimens taken during fasting by 50 mg. or more and (3) a blood sugar level at one hour which exceeds the half-hour level by 30 mg. or more. These criteria were fulfilled in all but 2 instances (20 tests for 16 diabetic patients), in which low, flat curves were obtained in the early, untreated state and in which high values during fasting were obtained months later (chart 5 illustrates 1 such instance). On the other hand, the curves of 2 patients with nondiabetic conditions fulfilled these criteria: L.G., chart 2, and D.N., chart 6. The former, an

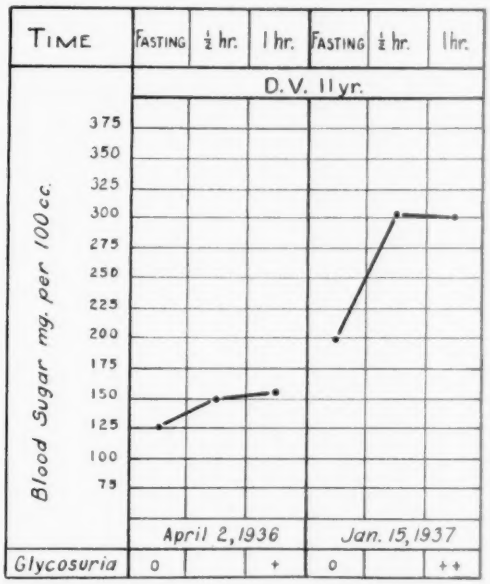

Chart 5.—Changing tolerance, as demonstrated by the one hour, two dose dextrose tolerance test. A low threshold type of curve appears at the onset of diabetes, but a much higher threshold for sugar is seen nine and one-half months later. The condition was well controlled by 19 units of regular insulin and 200 Gm. of carbohydrate at the beginning of treatment. After nine and one-half months of this diet 32 units of regular insulin was required to keep the condition equally well controlled.

epileptic patient, has been discussed; the latter had a clinical picture of hyperthyroidism, in which a diabetic type of curve is not unusual.

As to the claim that the blood and urine sugar values stand in quantitative relation to the severity of the diabetic involvement, for several reasons it appears that no definite conclusions can be drawn by comparing dextrose tolerance curves of different persons. In children there is a tendency for the level of the blood sugar in the morning during

fasting to rise with age and with duration of the diabetic condition, and this tendency should not necessarily be regarded as evidence of progressive involvement.[11] Judging from a review of the available data, the renal threshold in cases of diabetes appears to be a widely variable and individual matter unrelated to the severity of the diabetic condition.[12] These points are apparent in chart 4, which illustrates the dextrose tolerance tests for 4 patients with diabetic conditions of varying duration. All were receiving 175 Gm. of carbohydrate and between 1,990 and 2,120 calories. The doses of regular insulin

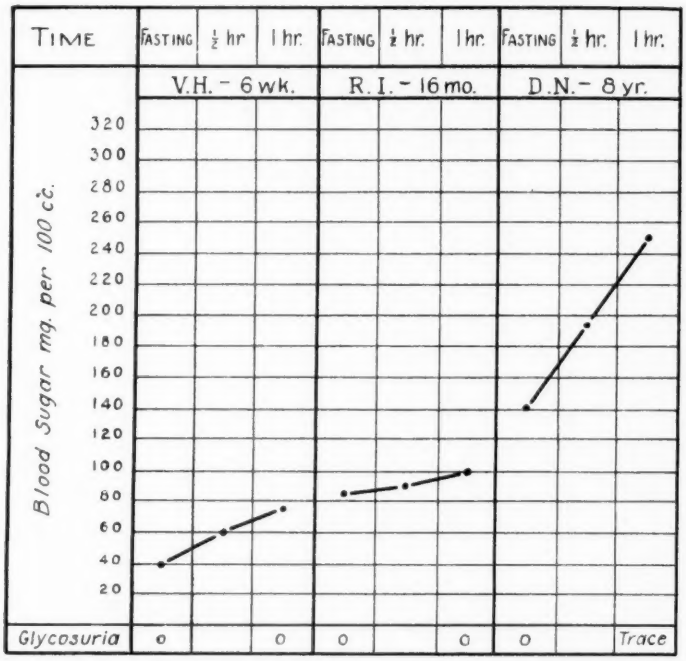

Chart 6.—The one hour, two dose dextrose tolerance test in other endocrine conditions. V.H. had convulsions associated with hypoglycemia. There is a slow rise in the blood sugar curve, with values in or near the hypoglycemic zone. R.I. has the low, flat type of curve seen with cretinism. D.N., a boy of 8 years with a toxic adenoma of the thyroid, showed a diabetic type of curve. The basal metabolic rate was + 41 per cent before thyroidectomy.

required to maintain 3 of the patients (E.S., A.M., and E.Y.) under an approximately equal degree of control were 58, 15 and 28 units, respectively. E.S. had a renal threshold at or below the 160 mg. level

11. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932.

12. Marble, A.: Treatment of Diabetes Mellitus in the Presence of High or Low Threshold for Sugar, M. Clin. North America **21**:427. 1937.

of the blood sugar during fasting, whereas A.M. was aglycosuric, with a blood sugar level of 200 mg. during fasting. The blood sugar curve of E.Y., with a diabetic state of one year's duration, was on a higher level than that of E.S., with an involvement of five years' duration, although the former patient required considerably less insulin. J.P., with a poorly controlled diabetic condition of twenty months' standing, demonstrated high blood sugar values.

A truer estimate of the quantitative relation between sugar values of the dextrose tolerance test and changes in the diabetic state appears available from a study of the individual patient at successive periods. D.V. (chart 5) illustrates the transition from a comparatively low threshold type of sugar tolerance curve at the beginning of treatment to a high threshold type of curve nine and one-half months later. Concomitantly, with an identical diet, the child's requirement of regular insulin rose from 19 to 32 units.

The one hour, two dose dextrose tolerance test should find application in the various nondiabetic conditions in children in which disturbances of carbohydrate metabolism are to be ruled out, such as benign glycosuria, and in conditions in which deviations of carbohydrate metabolism may be found, as in celiac disease, prematurity, malnutrition, cyclic vomiting, hypoglycemia due to pancreatic and extrapancreatic causes and endocrine dysfunction in general. In chart 6 are the blood sugar curves of 3 patients with abnormalities of endocrine function. V.H., a 6 week old infant, was admitted to St. Luke's Hospital with convulsive seizures. His blood sugar curve gave evidence of an increase in tolerance, with a total rise of only 35 mg. above the hypoglycemic level of 40 mg. during fasting. In general, however, dextrose tolerance tests have not been found significantly contributory to the diagnosis of functional hypoglycemia.[13] The blood sugar curves of R.I. and D.N. demonstrate the increased tolerance for sugar in cretinism and the reduced tolerance in hyperthyroidism, respectively, the latter patient showing a typical diabetic type of curve.

SUMMARY AND CONCLUSIONS

The one hour, two dose dextrose tolerance test previously found to be a specific, time-saving and convenient procedure for adults was applied to infants and children.

The technic of the original test was modified to suit this age period. The micromethod for determination of the blood sugar was found to be a reliable additional simplification of the procedure.

13. Rector, J. M., and Jennings, R. E.: Functional Hypoglycemia of Childhood, Am. J. Dis. Child. **53**:1012 (April) 1937.

One hundred and two tests were performed on 82 subjects, consisting of 30 controls, 16 patients with diabetes mellitus of varying degree and duration and 36 patients with nondiabetic conditions.

The characteristics of the normal response to the one hour, two dose dextrose tolerance test in a control group of subjects were found to be as follows: (1) a normal blood sugar level during fasting (average, 91 mg.); (2) a more or less steep rise at thirty minutes (10 to 63 mg.), and (3) a fall below the thirty minute blood sugar level at the sixty minute determination in 76.5 per cent of the tests and an elevation above the thirty minute value at sixty minutes in 23.5 per cent, the total rise in the blood sugar level in no instance exceeding the normal level during fasting by more than 80 mg.

Application of these diagnostic criteria to the group of patients with nondiabetic conditions did not yield any unaccountable deviations.

The one hour, two dose dextrose tolerance test performed for the group of diabetic patients revealed the following features: (1) a normal blood sugar level during fasting or one above the normal limits (120 mg.); (2) a more or less steep rise at thirty minutes; (3) a hyperglycemic level at sixty minutes, the total rise exceeding 80 mg., with an occasional exception in cases of early diabetes mellitus of the low threshold type, and (4) glycosuria in at least the sixty minute specimen.

Several abnormal curves were demonstrated for patients with nondiabetic conditions associated with deviations of normal carbohydrate metabolism.

The employment of the one hour, two dose dextrose tolerance test for infants and children demonstrated the important features of specificity, time saving and convenience. All these considered, the test offers an improved method for estimating dextrose tolerance in subjects of this age period.

GROWTH NORMS FROM BIRTH TO THE AGE OF FIVE YEARS

A STUDY OF CHILDREN REARED WITH OPTIMAL PEDIATRIC AND HOME CARE

JOHN GRAY PEATMAN, PH.D.
AND
REGINALD A. HIGGONS, M.D.
PORT CHESTER, N. Y.

Height-weight norms for boys and girls are presented here to meet a need long felt by many pediatricians, who have found most charts of growth norms for children up to 5 years of age unsatisfactory on two counts. In the first place, norms such as those of Woodbury [1] and of Baldwin and Wood [2] have appeared to be too low for children reared with optimal (or at least above the average for the population) pediatric and home care. In the second place, for such children there has been lacking an adequate set of norms of weights for varying heights at given months of age through the first 5 years of life.

We shall present (1) a description of the type of pediatric care given the boys and girls whose height-weight measurements were used; (2) a description of the type of feeding; (3) a statistical summary of the sample of subjects; (4) the height-weight norms which were obtained, and (5) comparisons of our norms with those of Woodbury, of Baldwin and Wood and of the New York State Department of Health, the last-mentioned values having been developed from data of Holt, Woodbury, Emerson and Manny, Crum, Smith, Baker and Lucas.[3]

TYPE OF PEDIATRIC CARE

Most infants are first seen at the age of 1 month. They are then seen routinely as follows: bimonthly from 1 to 3 months, monthly from 3 to 12 months, quarterly from 12 months to 2 years, semiannually from 2 to 5 years and annually from 5 years to puberty.

1. Woodbury, R. M.: Statures and Weights of Children Under Six Years of Age, Bureau Publication 87, United States Department of Labor, Children's Bureau, 1921.

2. Baldwin, B. T.: Physical Growth of Children from Birth to Maturity: Studies in Child Welfare, Iowa City, University of Iowa, 1921, vol. 1, no. 1. Baldwin, B. T., and Wood, T. D.: Weight-Height-Age Tables, Mother & Child (supp.) **4**:1, 1923.

3. Charts of Heights and Weights, New York State Department of Health, Division of Maternity, Infancy and Child Hygiene, October 1936.

All routine examinations are made with the child completely stripped. Such examinations include determinations of height, weight, circumferences of the head and chest, number of teeth and size of the fontanel; a rough estimation of the degree of muscle tone and tissue tone; inspection of the ears, eyes, nose, throat, superficial glands, genitals, feet and posture, if the child is able to stand; auscultation and percussion of the heart and the lungs; palpation of the abdomen; determination of the hemoglobin percentage every three months, and urinalysis once each year, unless it is otherwise indicated.

Each child receives diphtheria toxoid at the age of 8 months, a Schick test at 12 months, pertussis vaccine (Sauer) at from 12 to 15 months, smallpox vaccine at from 4 to 5 years and tetanus toxoid at school age or before, unless this is declined by the parents.

Sunbaths with the child stripped are given from April to October, and ultraviolet radiation from an air-cooled quartz mercury vapor arc lamp is given during the winter months, if indicated.

An excess of iron (in the form of iron and ammonium citrates) is administered routinely to all children whose hemoglobin percentage is below 80.

The home and school environment is carefully studied in each case, and any necessary adjustments are made, when possible, to insure ample rest and to prevent excessive or harmful stimulation.

TYPE OF FEEDING

The following summary shows the general principles behind the type of feeding used in these cases:

1. Ample caloric intake at all times:
   (*a*) Under 1 year of age, 50 to 75 calories per pound (0.5 Kg.) of body weight
   (*b*) Over 1 year of age, somewhat lower figures (35 to 60 calories per pound)
2. Relatively high protein intake:
   (*a*) For babies on a formula, 2 + ounces (59 cc.) of milk per pound per day
   (*b*) Later fortified by
      Egg yolk at about 3 months
      Vegetable protein at from 3½ to 4 months
      Meat and liver at about 5 months
      Milk and egg puddings after 6 months
   (*c*) Above one year, rather large amounts of meat daily, 1 or 2 eggs daily, cheese frequently, about 16 to 24 ounces (473 to 710 cc.) of milk daily in addition to the vegetable protein and milk and egg desserts
3. Relatively low total fluid intake, as reflected in consumption of liquid milk:
   (*a*) Infants' formulas never exceed 35 ounces (1,035 cc.) per day
   (*b*) At about 4 or 5 months the total is reduced to from 28 to 32 ounces (from 828 to 946 cc.) by omission of all night feedings
   (*c*) At about the 18 pound level of weight the total is reduced to about 24 ounces, when the child is placed on a three meal regimen
   (*d*) For children above 2 years, the average is restricted to 1 pint (473 cc.) of milk daily
4. Relatively high intake of solid food:
   (*a*) Cereal fed by spoon twice a day after the age of from 2 to 2½ months
   (*b*) Strained vegetables started at from 3 to 4 months

(*c*) For older infants and young children, the emphasis is always placed on solid food rather than milk. No infant or child is ever permitted to drink water with meals or ever urged to drink between meals

5. Relatively low carbohydrate:
   (*a*) The total sugar added to infants' formulas rarely exceeds 1 ounce (28 Gm.) and is never over 1½ ounces (43 Gm.)
   (*b*) Practically no sugar is ever added to foods except that used in cooking
   (*c*) Candy is always discouraged, and sweet preserves, etc., are on the list of forbidden foods
   (*d*) The cereal for supper is replaced by vegetables and egg frequently after 1 year and occasionally between 8 and 12 months
6. Relatively low fat:
   (*a*) No top milk mixtures are used
   (*b*) Extra butter and cream are used after 1 year only in the underweight group
   (*c*) Grease, mayonnaise and olive oil are always prohibited
7. Relatively high vitamin intake:
   (*a*) Orange juice is started at 4 weeks, with 1 ounce (30 cc.) daily. This is increased to 3 ounces (887 cc.) by 3 or 4 months and to 6 or 8 ounces (177 to 237 cc.) after 1 year. Cevitamic acid is used in corresponding amounts if orange juice is not tolerated
   (*b*) Cod liver oil or one of its substitutes is started at 4 weeks. By 2 months each child receives daily 9,000 or more units of vitamin A (U. S. P. XI) and 1,600 or more units of vitamin D (U. S. P. XI). At 4 months this dose is increased to a minimum of 20,000 units of vitamin A and 3,200 of vitamin D. After 8 months the amount varies from this minimum to a maximum of three times this quantity, depending on the condition of the child
   (*c*) The intake of vitamins B_1 and B_2 is often increased by the addition of yeast or rice polishings
   (*d*) The early and free addition of whole grain cereals, egg yolk and green vegetables further enhances the vitamin intake
8. The child is always encouraged to "grow up" as regards his food. Every child is weaned from the bottle by the age of 1 year if this is at all practicable, and many are off the bottle by 8 or 9 months. The child is encouraged to feed himself early. Excitement and company at meals are always discouraged. Foods are mixed together as much as possible until the child is from 18 months to 2 years of age. Eating is kept on the animalistic plane as long as possible. No mother is ever told to force any food or drink at any age.

STATISTICAL SUMMARY OF THE SAMPLE OF SUBJECTS

The measurements used in this study were taken from a group of children as well as the average, who were receiving routine pediatric care. Children who presented a feeding problem were not eliminated from the sample of subjects, since we aimed to have the children representative of patients seen in a normal pediatric office practice. We believe that the following account of our subjects justifies the

assertion that our norms have been derived from an adequate sample of boys and girls up to the age of 5 years, born of American parentage, reared in a suburban environment and receiving optimal private pediatric and home care.

One of the interesting points concerning the growth norms developed in this study is that in the case of both boys and girls (and for the average curves of both height and weight) our norms follow closely those of Woodbury [1] up through the third month of life. From that point there is a gradual and statistically significant increase of our curves over those of Woodbury (charts 3 and 4). It is logical that this increase should result from the data of our subjects, since they represent a sample drawn from an environment superior, in many of the variables affecting growth, to the average environment.

1. *Number of Subjects, Height-Weight Measures and Sex Groupings.*—Our norms were derived from 5,149 pairs of height-weight measurements, which were obtained from a total of 1,112 subjects. Of these measurements, 2,633 (51 per cent) were obtained from the records of 577 boys and 2,516 (49 per cent), from the records of 535 girls. There was therefore an average of 4.6 pairs of height-weight measurements per boy and 4.7 pairs per girl. The latter fact makes our sample more adequate than is usually the case for growth samples, as the norms have been obtained to a marked degree from growing subjects, i. e., from a partly continuous sample.

Fifty-nine subjects were eliminated from an original group of 1,171 because they were born of pregnancies shorter than the full term. Checking the data of these few subjects against the averages obtained from the group used, it was found that their inclusion with the latter would not have affected the norms noticeably during the first three years of life. After the age of 3 years no effect would be expected, in view of Mohr and Bartelme's [4] studies of the physical and mental growth of premature children.

2. *Environmental Background of Subjects.*—Practically all of the subjects lived in the towns of Rye, N. Y., and Greenwich, Conn., the few exceptions residing in nearby towns of Westchester County, N. Y. This area is suburban to New York. All of the subjects were patients in the private pediatric practice of one of us.

Of the total group of 1,112 subjects, it was possible definitely to classify 719 (65 per cent) of them on the basis of their home environment into one of three groups, defined as follows:

1. Lower middle class standard of living: Here the family income varies between $1,500 and $3,500 annually. The parents have nearly

4. Hess, J. H.; Mohr, G. J., and Bartelme, P. F.: Physical and Mental Growth of Prematurely Born Children, Chicago, University of Chicago Press, 1934.

all received at least a high school education, and many are college graduates. They live usually in small houses without servants. They are able to buy all necessary equipment for the care of the child, but they lack many luxuries.

2. Middle class standard of living: The parents of this group have an income of from $3,000 to $7,000 a year. They include a larger number of college graduates and persons in the professions and in small businesses. Most of them have homes with one or two servants and have no financial worries until they are met by a sudden large demand.

3. Wealthy standard of living: The parents of this group have an annual income of $7,000 and over. They usually have nurses to help

TABLE 1.—*Environmental Distribution of Subjects*

Environmental Category (Standard of Living)	Boys		Girls		Both	
	No.	%*	No.	%*	No.	%*
1. Lower middle class	155	21.6	142	19.7	297	41.3
2. Middle class	151	21.0	165	22.9	316	43.9
3. Wealthy class	46	6.4	60	8.3	106	14.7

* These are percentages of the total group of 719 environmental classified subjects.

TABLE 2.—*Distribution of Subjects by Parentage*

Parentage	Boys		Girls		Both	
	No.	%*	No.	%*	No.	%*
1. American	243	21.9	261	23.4	504	45.3
2. Foreign	98	8.8	81	7.3	179	16.1
3. Unclassified	236	21.2	193	17.4	429	38.6

* These are percentages of the total group of 1,112 subjects.

raise their children. Their homes are likely to be spacious and well adapted for any type of special care. Money is no object with these parents if they can be convinced of the need for the expenditure.

The 719 subjects thus classified were distributed as shown in table 1.

From table 1 it will be seen that the percentages of subjects in the lower middle class and the middle class are about the same (totaling together about 85 per cent of the entire group), whereas about 15 per cent of the children are in the wealthy class. As already indicated, children reared by the standards of the lower middle class probably received as adequate care in the basic environmental variables making for growth as children of the wealthy class.

3. *Nationality of Subjects.*—The great majority of the subjects were of American parentage, with North European stock apparently predominating. The distribution of the parentage of the total group of subjects is presented in table 2.

Of the 1,112 subjects in table 2, 429 are grouped as unclassified because of insufficient knowledge about their parents' nationality. Those of foreign parentage are mainly of Italian, Jewish or Polish stock. They are separated for analytical purposes because in height they possibly run below the average of North European stocks.

If the ratio (about 3 to 1) of American to foreign parentage is true of the unclassified group, then approximately three quarters of the latter are of American parentage. This means that of the total group of subjects, about 75 per cent are of American and 25 per cent of foreign parentage. This ratio of 3 to 1 is possibly representative of private pediatric practice in areas suburban to our larger cities. In any event, the height-weight data for each month were so organized that it was possible to ascertain whether the addition of the groups of foreign and unclassified parentage to the American group made any

TABLE 3.—*Distribution of Measurements by Age Group*

Age in Months	No. of Measurements		Age in Months	No. of Measurements	
	Boys	Girls		Boys	Girls
1.....	150	129	12.....	144	152
2.....	172	165	15.....	141	117
3.....	183	160	18.....	108	106
4.....	170	162	21.....	87	85
5.....	160	159	24.....	101	108
6.....	156	147	30.....	101	100
7.....	141	137	36.....	93	82
8.....	130	132	42.....	65	71
9.....	122	116	48.....	63	74
10.....	121	109	54.....	43	48
11.....	115	96	60.....	67	61

Total number of measurements of boys, 2,633; of girls, 2,516

significant difference in the norms. With such an addition, there were of course slight fluctuations in the average measurements; however, in none of the age groups were the correlations between height and weight or the average heights and weights markedly affected. In fact, the addition of the unclassified group served to strengthen the adequacy of the original sample of data, since the additional subjects, when analyzed separately at each age group, gave results similar to those of the subjects of American parentage.

4. *Age Group Samples.*—In pediatric practice, infants are seen more often near the monthly birthday than around the middle of the month. Consequently, all data were tabulated in respect to the monthly birthday during the first year. Thus the age group of 4 months includes subjects measured at an age between 3½ and 4½ months. After the age of 12 months no measurements were recorded unless obtained within one month below or above the age group considered.

Table 3 gives the number of height-weight measurements for each age group, differentiated for sex. As previously noted, since there

were 577 boys, the average number of height-weight pairs of measurements per boy was 2,633/577, or 4.6; for the 535 girls, the number was 2,516/535, or 4.7.

As to the number of measurements for each age group, it is apparent from table 3 that the samples are more adequate for the first three years than for the last two. However, as revealed in the graphs of the next section (charts 1 and 2), the errors for height which might arise from the smaller samples tended to be at a minimum, and those for weight were reduced to a minimum in the curves fitted to the original trend of the data.

5. *Conditions of Measurement.*—The conditions under which all measurements were made will be briefly described.

(*a*) Height: Up to the age of 3 years height is measured with the child recumbent on a flat, hard surface. A steel tape is stretched along this surface, and the distance is taken from points squared off at the sole of the heel and at the vertex of the skull. After the age of 3 years height is measured with the usual rod for the erect position.

(*b*) Weight: All weights are measured on standard Fairbanks balance scales, with the child sitting in the trough as an infant and standing on a platform as soon as he is able.

All measurements used in this study were made personally by the pediatrician.

THE HEIGHT-WEIGHT NORMS

The data on height and weight for boys and girls are presented graphically in charts 1 and 2. The curves representing the original data as well as the curves smoothed for errors are shown. All of these graphs, especially those for height, reveal the adequacy of our sample by the marked regularity of the curves based on raw data.

Table 4 gives the height and weight averages of the original data and of the smoothed curves. The differences between the two sets of averages are given in the last two columns of this table in order to indicate exactly the deviations of the original from the smoothed curves.

In tables 5 and 6 our norms of weight for a given height at a given age are presented for boys and girls. These norms have been established, first, in relation to the smoothed averages of table 4 and, second, in relation to the estimated regression of weight on height as derived from the correlation between these two variables at each age level and for boys and girls. Necessary adjustments have been made for errors in sampling. Were there no correlation between the subjects' height and weight for a given age, the best prediction of weight for any given height would of course be the average weight for the given age group. However, as is well known, there is a definite correlation between height and weight for a given age. For older age

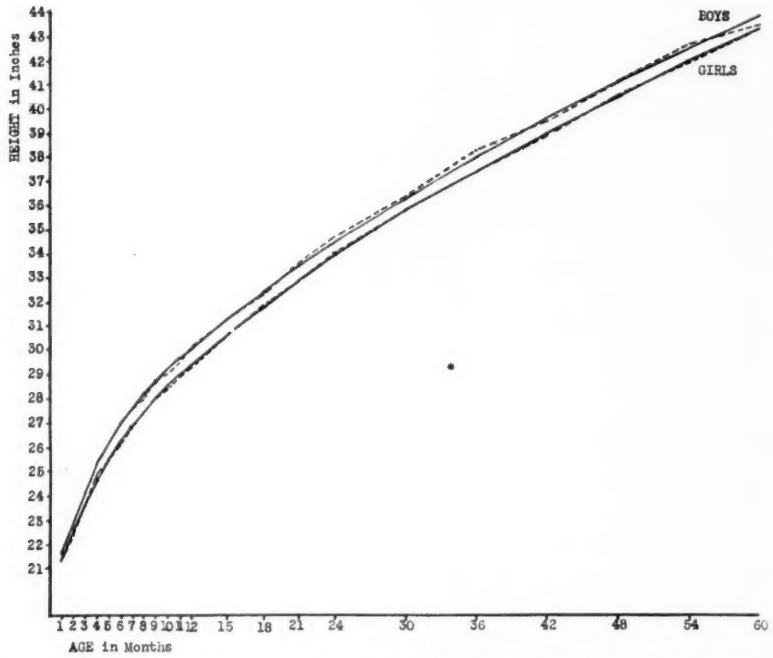

Chart 1.—Curves of growth in height, plotted to the original averages and smoothed for errors in sampling.

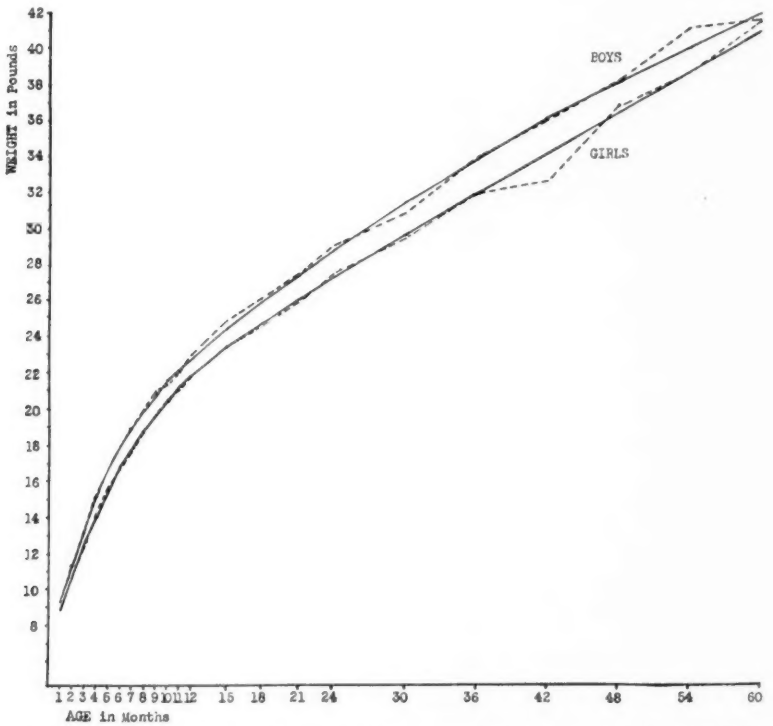

Chart 2.—Curves of growth in weight, plotted to the original averages and smoothed for errors in sampling.

groups, correlations have been found to range from 0.50 to 0.75, according to Garrett and Schneck.[5] The correlations between weight and height for the 22 age groups, boys and girls, of the present study ranged from 0.56 to 0.84, with the median correlation 0.70.

TABLE 4.—*Comparison of Original and Smoothed Height-Weight Averages*

Age in Months	Original Averages		Smoothed Averages		Differences Between Original and Smoothed Averages	
	Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds
			Boys			
1	21.6	9.3	21.6	9.3	0	0
2	22.9	11.4	22.9	11.4	0	0
3	24.2	13.4	24.2	13.4	0	0
4	25.4	15.4	25.4	15.2	0	−0.2
5	26.2	16.8	26.2	16.8	0	0
6	27.0	18.0	27.0	18.0	0	0
7	27.6	19.0	27.6	19.0	0	0
8	28.0	20.0	28.1	19.9	+0.1	−0.1
9	28.8	20.9	28.7	20.7	−0.1	−0.2
10	29.0	21.3	29.2	21.5	+0.2	+0.2
11	29.5	22.0	29.7	22.1	+0.2	+0.1
12	30.2	23.0	30.1	22.8	−0.1	−0.2
15	31.3	24.8	31.3	24.4	0	−0.4
18	32.3	26.1	32.4	25.9	+0.1	−0.2
21	33.6	27.5	33.5	27.4	−0.1	−0.1
24	34.7	29.1	34.5	28.8	−0.2	−0.3
30	36.4	30.8	36.3	31.4	−0.1	+0.6
36	38.3	33.8	38.0	33.7	−0.3	−0.1
42	39.5	35.9	39.6	36.0	+0.1	+0.1
48	41.1	38.1	41.1	38.0	0	−0.1
54	42.7	41.0	42.5	39.8	−0.2	−1.2
60	43.5	41.4	43.9	41.7	+0.4	+0.3
			Girls			
1	21.3	8.9	21.2	8.9	0	0
2	22.4	10.8	22.5	10.9	+0.1	+0.1
3	23.7	12.5	23.7	12.7	0	+0.2
4	24.9	14.5	24.7	14.2	−0.2	−0.3
5	25.5	15.7	25.5	15.6	0	−0.1
6	26.1	16.7	26.2	16.8	+0.1	+0.1
7	26.8	17.7	26.8	17.8	0	+0.1
8	27.4	18.8	27.4	18.8	0	0
9	28.0	19.7	28.0	19.7	0	0
10	28.4	20.6	28.5	20.5	+0.1	−0.1
11	28.9	21.0	29.0	21.2	+0.1	+0.2
12	29.3	21.8	29.4	21.8	+0.1	0
15	30.6	23.4	30.6	23.4	0	0
18	31.9	24.6	31.8	24.7	−0.1	+0.1
21	32.9	25.8	32.9	26.0	0	+0.2
24	34.1	27.4	34.0	27.2	−0.1	−0.2
30	35.8	29.4	35.8	29.5	0	+0.1
36	37.4	31.8	37.4	31.8	0	0
42	38.9	32.6	39.0	34.1	+0.1	+1.5
48	40.6	36.7	40.5	36.4	−0.1	−0.3
54	41.9	38.6	42.0	38.7	+0.1	+0.1
60	43.4	41.4	43.4	40.8	0	−0.6

As the correlation between two variables decreases toward 0 from a perfect relation of 1, the accuracy of prediction of the measurements of one variable from given values of the other falls off rapidly. Thus a correlation of 0.87 is necessary to give an accuracy in predictive estimates halfway between the invariance of perfect correlation and the

5. Garrett, H. E., and Schneck, M. R.: Psychological Tests, Methods and Results, New York, Harper & Brothers, 1933.

TABLE 5.—*Boys' Height-Weight Norms: Average Weight for Given Height; Ages One to Sixty Months**

Height in Inches	Age in Months																					
	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	30	36	42	48	54	60
19.5	6½	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
20.0	7⅛	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
20.5	7¾	8¼	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
21.0	8½	8⅞	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
21.5	9⅛	9½	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
22.0	9¾	10¼	10½	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
22.5	10⅜	10⅞	11⅛	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
23.0	11	11½	11¾	12⅛	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
23.5	11¾	12⅛	12½	12¾	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
24.0	12⅜	12¾	13⅛	13⅜	13⅝	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
24.5	....	13⅜	13¾	14	14½	14¾	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
25.0	....	14	14⅜	14¾	15⅛	15⅜	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
25.5	....	....	15	15⅜	15¾	16	16⅜	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
26.0	....	....	15⅝	16	16⅜	16¾	17	17½	....	....	....	....	....	....	....	....	....	....	....	....	....	....
26.5	....	....	16¼	16⅝	17	17⅜	17⅝	18⅛	18¼	....	....	....	....	....	....	....	....	....	....	....	....	....
27.0	....	....	....	17¼	17¾	18	18¼	18⅝	18¾	19	....	....	....	....	....	....	....	....	....	....	....	....
27.5	....	....	....	17⅞	18⅜	18⅝	18⅞	19⅛	19⅜	19½	19⅞	....	....	....	....	....	....	....	....	....	....	....
28.0	....	....	....	....	19	19¼	19½	19¾	20	20⅛	20⅜	20½	....	....	....	....	....	....	....	....	....	....
28.5	....	....	....	....	19⅝	19⅞	20⅛	20¼	20½	20⅝	20⅞	21⅛	21¼	....	....	....	....	....	....	....	....	....
29.0	....	....	....	....	....	20½	20⅝	20⅞	21⅛	21¼	21⅜	21½	21¾	....	....	....	....	....	....	....	....	....
29.5	....	....	....	....	....	21⅛	21¼	21½	21⅝	21¾	21⅞	22⅛	22¼	22⅝	....	....	....	....	....	....	....	....
30.0	....	....	....	....	....	....	21⅞	22	22¼	22⅜	22½	22⅝	22⅞	23¼	....	....	....	....	....	....	....	....
30.5	....	....	....	....	....	....	....	22⅝	22¾	23	23⅛	23¼	23½	23⅝	23⅞	....	....	....	....	....	....	....
31.0	....	....	....	....	....	....	....	....	23⅜	23½	23⅝	23¾	24	24¼	24½	....	....	....	....	....	....	....
31.5	....	....	....	....	....	....	....	....	....	24	24¼	24⅜	24⅝	24⅞	25	25¼	....	....	....	....	....	....
32.0	....	....	....	....	....	....	....	....	....	....	24¾	24⅞	25¼	25½	25⅝	25¾	....	....	....	....	....	....
32.5	....	....	....	....	....	....	....	....	....	....	....	25½	25⅞	26	26¼	26⅜	....	....	....	....	....	....
33.0	....	....	....	....	....	....	....	....	....	....	....	....	26⅜	26⅝	26¾	27	....	....	....	....	....	....
33.5	....	....	....	....	....	....	....	....	....	....	....	....	27	27⅛	27⅜	27½	27¾	....	....	....	....	....
34.0	....	....	....	....	....	....	....	....	....	....	....	....	27½	27¾	28	28⅛	28⅞	....	....	....	....	....
34.5	....	....	....	....	....	....	....	....	....	....	....	....	....	28¼	28½	28¾	29	....	....	....	....	....
35.0	....	....	....	....	....	....	....	....	....	....	....	....	....	28⅞	29⅛	29⅜	29⅝	30	....	....	....	....
35.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	29⅝	30	30¼	30⅝	....	....	....	....
36.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	30¼	30⅝	30⅞	31¼	....	....	....	....
36.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	30⅞	31¼	31⅝	31⅞	....	....	....	....
37.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	31⅞	32¼	32½	32⅞	....	....	....
37.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	32½	32¾	33⅛	33½	....	....	....
38.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	33½	33¾	34⅛	34½	....	....
38.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	34⅛	34⅜	34¾	35	....	....
39.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	34¾	35	35¼	35⅝	....	....
39.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	35⅝	35⅞	36⅛	36¼	....
40.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	36¼	36½	36¾	36⅞	37⅛
40.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	36⅞	37⅛	37¼	37½	37¾
41.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	37½	37⅝	37⅞	38	38¼
41.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	38¼	38½	38⅝	38⅞
42.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	38⅞	39	39⅛	39½
42.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	39⅜	39½	39⅝	40
43.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	40⅛	40¼	40⅝
43.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	40⅝	40⅞	41¼
44.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	41⅛	41⅜	41⅞
44.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	41¾	42	42⅜
45.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	42⅝	43
45.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	43¼	43⅝
46.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	43⅞	44¼
46.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	44⅞
47.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	45½
47.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	46⅛

* All weights are given in pounds to the nearest fraction in eighths.
In using this table of norms, take the child's height without shoes first, and then locate the estimated weight for that height in the column of his age (to the nearest monthly birthday).

Height in Inches	Age in Months																					
	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	30	36	42	48	54	60

Height in Inches	Age in Months																					
	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	30	36	42	48	54	60
19.0	6	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
19.5	6⅝	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
20.0	7⅜	7¾	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
20.5	8	8⅜	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
21.0	8½	9	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
21.5	9⅛	9⅝	10	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
22.0	9¾	10¼	10½	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
22.5	10⅜	10⅞	11⅛	11½	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
23.0	11	11½	11¾	12⅛	12¾	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
23.5	11⅝	12⅛	12½	12¾	13⅛	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
24.0	....	12¾	13⅛	13⅜	13¾	14	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
24.5	....	13⅜	13¾	14	14⅜	14⅝	15⅛	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
25.0	....	14	14⅜	14⅝	15	15¼	15⅝	16	....	....	....	....	....	....	....	....	....	....	....	....	....	....
25.5	....	....	15	15¼	15⅝	15⅞	16⅛	16½	17	....	....	....	....	....	....	....	....	....	....	....	....	....
26.0	....	....	15⅝	15⅞	16¼	16½	16¾	17⅛	17½	17⅞	....	....	....	....	....	....	....	....	....	....	....	....
26.5	....	....	....	16½	16⅞	17⅛	17⅜	17¾	18⅛	18⅜	18⅝	....	....	....	....	....	....	....	....	....	....	....
27.0	....	....	....	17⅛	17½	17¾	18	18¼	18⅝	18⅞	19⅛	19¼	....	....	....	....	....	....	....	....	....	....
27.5	....	....	....	....	17⅞	18⅜	18⅝	18⅞	19¼	19⅝	19¾	19⅞	....	....	....	....	....	....	....	....	....	....
28.0	....	....	....	....	18¾	19	19¼	19½	19¾	20	20¼	20⅜	20⅝	....	....	....	....	....	....	....	....	....
28.5	....	....	....	....	....	19⅝	19⅞	20	20¼	20½	20¾	20⅞	21⅛	....	....	....	....	....	....	....	....	....
29.0	....	....	....	....	....	....	20⅜	20½	20¾	21	21¼	21⅜	21⅝	22	....	....	....	....	....	....	....	....
29.5	....	....	....	....	....	....	....	21⅛	21⅜	21½	21¾	21⅞	22¼	22½	....	....	....	....	....	....	....	....
30.0	....	....	....	....	....	....	....	....	21⅞	22	22¼	22⅜	22¾	23	23¼	....	....	....	....	....	....	....
30.5	....	....	....	....	....	....	....	....	22⅜	22½	22¾	22⅞	23¼	23½	23⅝	....	....	....	....	....	....	....
31.0	....	....	....	....	....	....	....	....	....	23⅛	23¼	23⅜	23¾	24	24⅛	24¼	....	....	....	....	....	....
31.5	....	....	....	....	....	....	....	....	....	....	23¾	23⅞	24¼	24½	24⅝	24¾	....	....	....	....	....	....
32.0	....	....	....	....	....	....	....	....	....	....	....	24⅜	24¾	25	25⅛	25¼	....	....	....	....	....	....
32.5	....	....	....	....	....	....	....	....	....	....	....	....	25¾	25½	25⅝	25¾	....	....	....	....	....	....
33.0	....	....	....	....	....	....	....	....	....	....	....	....	25⅞	26	26⅛	26¼	26⅜	....	....	....	....	....
33.5	....	....	....	....	....	....	....	....	....	....	....	....	26⅜	26½	26⅝	26¾	26⅞	....	....	....	....	....
34.0	....	....	....	....	....	....	....	....	....	....	....	....	....	27	27⅛	27¼	27½	....	....	....	....	....
34.5	....	....	....	....	....	....	....	....	....	....	....	....	....	27½	27⅝	27¾	28	28¼	....	....	....	....
35.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	28⅛	28¼	28⅝	28⅞	....	....	....	....
35.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	28⅝	28⅞	29¼	29½	....	....	....	....
36.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	29⅜	29¾	30	30¼	....	....	....
36.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	29⅞	30⅜	30⅝	30⅞	....	....	....
37.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	30⅜	30⅞	31¼	31½	31⅞	....	....
37.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	31½	31⅞	32⅛	32¼	....	....
38.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	32⅛	32½	32¾	33	....	....
38.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	32¾	33	33⅜	33⅝	34¼	....
39.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	33⅝	34⅛	34⅜	34⅞	....
39.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	34¼	34¾	35	35⅝	35⅞
40.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	34⅞	35⅝	35¾	36⅛	36½
40.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	36⅛	36⅜	36¾	37⅛
41.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	36¾	37	37⅜	37¾
41.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	37⅜	37⅝	38	38⅜
42.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	38	38¼	38¾	39⅛
42.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	38⅞	39⅜	39¾
43.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	39½	40	40⅜
43.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	40	40⅝	41
44.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	40⅝	41¼	41⅝
44.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	41⅞	42¼
45.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	42½	42⅞
45.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	43⅛	43½
46.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	44⅛
46.5	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	44¾
47.0	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	45⅜

* All weights are given in pounds to the nearest fraction in eighths.

In using this table of norms, take the child's height without shoes first, and then locate the estimated weight for that height in the column of her age (to the nearest monthly birthday).

complete lack of relation indicated by zero correlation. In making predictive estimates, however, norms are established for what will happen in the long run, or on the average. Consequently, for useful height-weight norms, correlations of around 0.70 or better have a considerable efficiency for predictive estimates of weight from height, or of height from weight. Our norms, then, represent estimates of the average regression of weight on height for given ages. In some of the height-weight charts commonly used, norms apparently have been set up without due regard to the amount of noncorrelation between the two variables, the tendency being to assume a practically perfect relation. This gives a spurious spreading of weights at the extreme heights for a given age, whereas in fact the lower the correlation between these variables the greater the tendency for the average estimates of weights

TABLE 7.—*Height-Weight Averages for Boys and Girls One to Sixty Months of Age*

Age in Months	Boys		Girls	
	Height, Inches	Weight, Pounds	Height, Inches	Weight, Pounds
1	21.6	9.3	21.3	8.9
2	22.9	11.4	22.5	10.9
3	24.2	13.4	23.7	12.7
4	25.4	15.2	24.7	14.2
5	26.2	16.8	25.5	15.6
6	27.0	18.0	26.2	16.8
7	27.6	19.0	26.8	17.8
8	28.1	19.9	27.4	18.8
9	28.7	20.7	28.0	19.7
10	29.2	21.5	28.5	20.5
11	29.7	22.1	29.0	21.2
12	30.1	22.8	29.4	21.8
15	31.3	24.4	30.6	23.4
18	32.4	25.9	31.8	24.7
21	33.5	27.4	32.9	26.0
24	34.5	28.8	34.0	27.2
30	36.3	31.4	35.8	29.5
36	38.0	33.7	37.4	31.8
42	39.6	36.0	39.0	34.1
48	41.1	38.0	40.5	36.4
54	42.5	39.8	42.0	38.7
60	43.9	41.7	43.4	40.8

for varying heights at a given age to regress, or to draw in to the average weight for the age group.

Since height-weight norms represent average or long run expectancy, an estimated weight for a given height at a given age has of course a range of normal variation for the healthy child. Faber [6] and Grandprey [7] suggested the 10 to 90 percentile range as possibly indicating the limits of such variation in the case of healthy children. Using Woodbury's [1] data, Grandprey obtained the values of the tenth and

6. Faber, H. K.: Variability in Weight for Height in Children of School Age, Am. J. Dis. Child. **30**:328-335 (Sept.) 1925.

7. Grandprey, M. B.: Range of Variability in Weight and Height of Children Under Six Years of Age, Child Development **4**:26-35, 1933.

ninetieth percentiles for all age groups. In the case of both boys' and girls' weights, these values of Grandprey are approximately 2½ to 3+ pounds (0.7 to 1.3 Kg.) above and below the averages of the age groups of the first year, 3½ to 4½ pounds (1.5-2 Kg.) for the second and third years and 4½ to nearly 5½ pounds (2 to 2.5 Kg.) for the fourth and fifth years. These ranges of variation are in relation to the average weights of given age groups. Whether they would apply to the averages of our data or to estimated weights for given heights at a given age has not been determined. We hope to present such an analysis in a future article.

We thought it might be of interest to develop a separate table from the data of table 4, indicating the average height and weight for each age group of the boys and girls of our sample. Averages of the smoothed data were used; the results are presented in table 7.

COMPARISONS OF OUR NORMS WITH THOSE OF WOODBURY, BALDWIN AND WOOD, AND THE NEW YORK STATE DEPARTMENT OF HEALTH

In charts 3 and 4 our average height and weight curves for boys and girls are compared with those for similar ages set up from the height-weight tables of Woodbury.[1]

The data for Woodbury's norms were obtained from a fairly heterogeneous sample of the United States. Over 2,000,000 records were sent to him at Washington from all over the country during Children's Year (1918). Of the 2,000,000 records, 172,000 satisfied his 4 selective criteria: (1) Each child's record card was signed by a physician, (2) no child had serious defects, (3) each child was weighed and measured in the nude and (4) all essential queries on each card were answered. About 3 per cent of the group were Negroes, and both parents of 69 per cent were born in the United States. The Southern states were underrepresented, one fifth of the records coming from Iowa and the bulk of the remainder from California and from the North-East-Central states. Although Woodbury's subjects possibly came from an environment better than the average, as far as the United States as a whole is concerned, competent and continuously adequate pediatric care, as earlier described, was not a relatively constant factor for all subjects.

The most striking feature of the comparison between Woodbury's curves and ours, as mentioned previously, is that in both height and weight the subjects of the present study start at about the same average point (slightly lower). However, after the third month our subjects slowly but steadily increase in average height and weight above the averages of Woodbury's subjects, maintaining this increase throughout

the balance of the five year period under study. Beginning with the fourth month for both boys and girls, the average difference at each age between Woodbury's weight averages and ours is statistically significant. That is, each average difference is more than three times the standard error of the difference.[8] Similarly, for height, the average

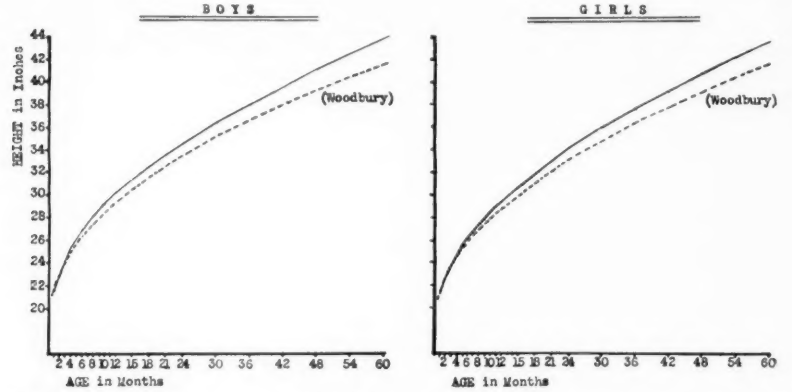

Chart 3.—Curves of growth in height: a comparison of our norms with those of Woodbury.[1]

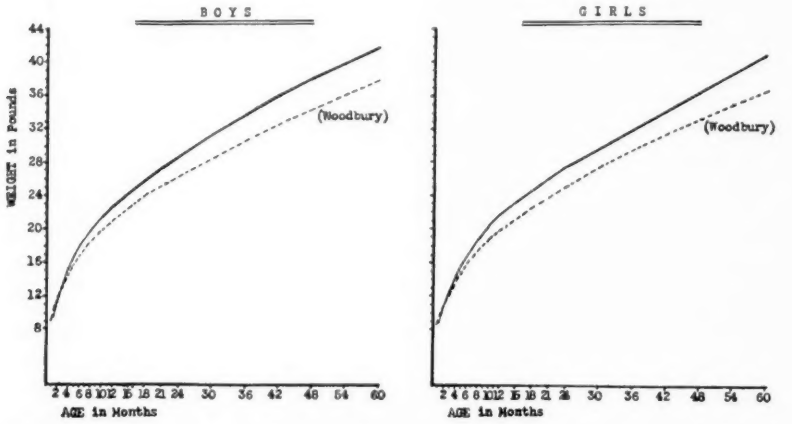

Chart 4.—Curves of growth in weight: a comparison of our norms with those of Woodbury.[1]

differences are statistically significant beginning with the fifth month. It may be obvious from the divergent nature of the curves in charts 3

8. This type of statistical comparison is made possible by the fact that Woodbury gives in tables 2 and 3 of his monograph the standard deviations of all distributions used as the basis of his averages. The curves of his averages, plotted in our charts 3 and 4, are derived from his smoothed averages of tables 2 and 3, just mentioned, except that after thirty-six months the corrected averages of table 31, page 76 of his monograph, were used. These corrections were made as the result of eliminating subjects with certain kinds of physical defects.[1]

and 4 that these average differences are increasingly significant through the age of 5 years.

As suggested earlier, these differences in the trends of the two sets of norms are possibly attributable to more adequate pediatric and home care for our subjects in such variables as diet, sunshine, exercise and rest. We believe that inheritance is not a logical explanation of the differences because of the practical identity of the height and weight averages for the earlier months.

A comparison of our height and weight averages with those of Baldwin and Wood,[2] and of our height curves (average weights for given ages are not presented in the chart) with those of the New York State Department of Health [3] gives results similar to those just described for Woodbury's norms. The norms of Baldwin and Wood and those of New York State (the latter having been based in part on those of Woodbury) give height and weight curves for both sexes practically identical with those of Woodbury, except that after the third year the height curves of Baldwin and Wood tend to be about 1 inch (2.5 cm.) lower than those of Woodbury. Since the curves of these two sets of norms are so similar to Woodbury's curves, we believe that charts 3 and 4 are adequate for comparison.

SUMMARY

A study is offered of 5,149 height-weight pairs of measurements of 1,112 boys and girls from 1 to 60 months of age, who live in a suburban area of New York and are subject to a relatively optimal degree of private pediatric care and home supervision.

We have presented norms of growth derived from this sample of measurements.

A comparison of our norms with those of other investigators reveals that our subjects, after the age of 3 months, are increasingly above the average in height and weight for the given ages.

We believe that increases in the height and weight of our subjects over the norms of other investigators are attributable to a relatively optimal degree of pediatric care and home supervision.

264 King Street.

EVIDENCES OF DISTURBED PRENATAL AND NEONATAL GROWTH IN BONES OF INFANTS AGED ONE MONTH

LESTER WARREN SONTAG, M.D.
YELLOW SPRINGS, OHIO

During examination of the skeletal roentgenograms of ninety-eight children taken at the age of 1 month I have observed phenomena in the lateral pictures of the tarsal bones. I am unable to find a description and discussion of some of these phenomena in the literature. A description of these variations in appearance is presented here because I believe that the presence or absence of certain of them may depend on the effects of the birth process or the infant's adjustment to its neonatal environment.

Since the phenomena observed consist of bands or rings in the nuclei of the tarsal bones, it seems desirable to present first such descriptions of bands and rings as are to be found in the literature, together with a discussion of their etiology.

Increased density of the bone at the periphery or outer layer of tarsal and carpal bones of children, which on roentgen examination has the appearance of a white ring encircling the nucleus, has been described by a number of observers. Wimberger [1] described this condition, accompanied by ground glass atrophy of the central portion, as occurring in scurvy. Bromer [2] and others have described a similar ring, but with a moth-eaten appearance of the central portion of the nucleus, in congenital syphilis. The same type of ring, but without loss of structure in the central portion of the nucleus, frequently occurs in rickets, particularly during the healing stage (Bromer,[2] Wimberger [3]). All these so-called rings appear at the extreme outer border of the bones and actually form the periphery, as seen on the roentgenograms. In the case of severe rickets and probably in the cases of both scurvy and syphilis, they apparently represent the heavy layer of mineral temporarily deposited in the layer of cartilage which immediately surrounds the invading osteoblasts. In the case of severe rickets and probably

From the Samuel S. Fels Research Institute, Antioch College.

1. Wimberger, H.: Zur Diagnose des Säuglingsskorbuts, Ztschr. f. Kinderh. **36**:279, 1923.

2. Bromer, Ralph S.: Demonstration of roentgenograms to the author.

3. Wimberger, H.: X-Ray Diagnosis of Rickets, Lancet **2**:11 (July 1) 1922.

in the cases of both scurvy and syphilis, the bone formed after treatment may be of a more dense nature than that of the original nucleus, so that it gives the appearance of a nucleus within a nucleus. In this instance the outer band of bone may be 5 or 10 mm. broad and may show a finer structure than the inner nucleus, with a much greater concentration of lime salts. Lewin described such a condition in a 2½ year old girl.

The most interesting type of ring found in my group of cases is different from any of those just described. The ring appears as a fine

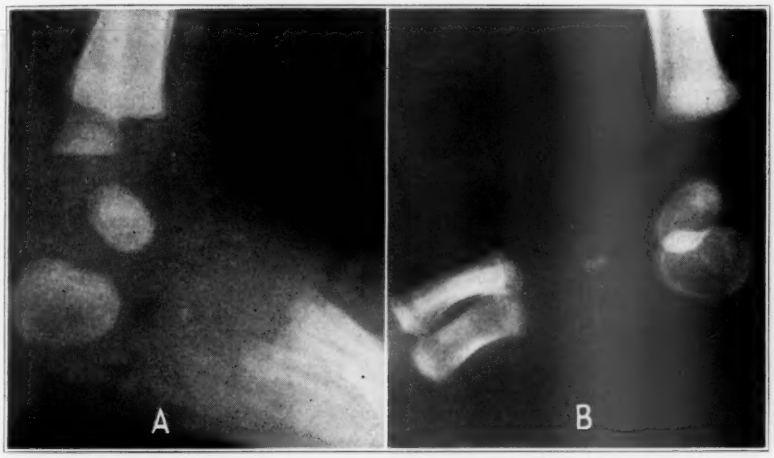

Fig. 1.—Roentgenograms taken at the age of 1 month, showing white lines or striae about 1 mm. from the peripheries of the calcaneus and talus. These white lines conform with the peripheries of the bones in roentgenograms taken at birth.

Fig. 2.—*A*, diagram of the broad outer band or temporary zone of calcification found at the age of 1 month; *B* represents the white line or striae just inside the periphery of the bone at the age of 1, 2 or 3 months. A transition from *A* to *B* has frequently been observed.

white line a fraction of a millimeter in width which follows the periphery of the talus or of the calcaneus but remains from 1 to 2 mm. inside it. The area between the line and the periphery appears to be of approximately the same structure and density as that of the central

portion of the nucleus. It presents much the same appearance as do the fine striae often found in the long bones of children. Consideration of the rate of growth and examination of roentgenograms made at birth indicate that the factor which caused this line occurred approximately at the time of birth. The basis for this conclusion will be discussed in more detail later in this paper. Fifty-four such cases exhibit this phenomenon. Figure 1 shows two of the roentgenograms. Figure *2 B* is a diagrammatic sketch of a tarsal nucleus which showed the white line.

Eight of the ninety-eight infants showed not a fine white line inside the periphery but a broad band 1 or 2 mm. wide which formed the

Fig. 3.—Roentgenogram taken at the age of 1 month, showing an outer white band or thickened temporary zone of calcification in the calcaneus. In the talus the band is beginning to resolve itself into a white line.

periphery of the bone. This band, which is occasionally seen at later ages, is apparently a somewhat thickened temporary zone of calcification. It was visible in none of the roentgenograms made at birth. Comparison of roentgenograms made at birth with those made at the age of 1 month indicates that the band represents about that portion of the nucleus which grows during the first month. Figure 3 shows this thickened temporary zone or band, and figure *2 A* is a diagrammatic sketch of it.

In addition to the two types of band or line already described, both of which are formed at or after birth, a third variety, which to judge from its size and location must be formed a considerable period before

birth, is not infrequently seen. This type is usually characterized at birth by a dense white nucleus within a total tarsal nucleus. The dense area, which may be round or oval, as seen in the roentgenogram, is usually less than 5 mm. in its greatest diameter. It may present a homogeneous appearance at birth, or there may be evidence of a beginning central involution, so that the area might be described as a heavy

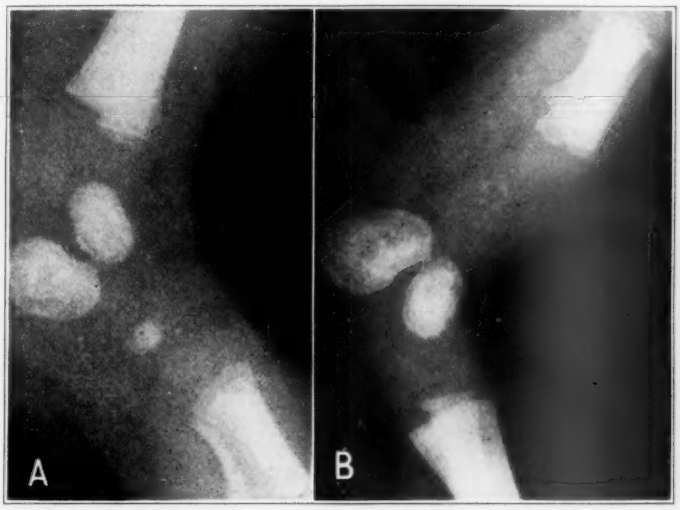

Fig. 4.—Roentgenograms taken at the age of 1 month, showing dense central nuclei in the calcaneus and talus. These nuclei are undergoing a fading process, which has begun centrally. In *A* there is also a broad temporary zone of calcification about the periphery of each bone, while in *B* it is present but is much narrower and less well defined.

Fig. 5.—*A* represents the hard central nucleus frequently observed at birth. *B* represents the beginning of fading or involution, which starts in the center, often seen at the age of 1 month but sometimes at birth. *C* represents the almost complete disappearance of this nucleus at the age of 1 or 2 months, only an indistinct outline of its border being seen. *B* and *C* also show the thickened temporary zone of calcification and its transition to a white line or stria.

irregular band. At the age of 1 month the involution frequently has progressed so as to give even more clearly the appearance of an irregular band in the center of the nucleus. Involution or absorption may

and frequently has progressed so far at 1 month that only a fine white line comparable to that first described (fig. 1) remains, except that this line encloses a small area near the center of the bone instead of being found just inside the periphery. This central nucleus or ring may be found without either the postnatal bands or the rings, or it may be found in conjunction with either. In figure 4 the center of the nucleus is beginning to fade, and there is a thickened temporary zone of calcification about its periphery; figure 5 shows diagrammatically its transitional changes from birth to the age of 1 month.

Apparently none of the phenomena described is the result of syphilis, rickets or scurvy, which are usually responsible for the rings or bands found in the tarsal bones of older children. For all the mothers of these infants Wassermann tests were done during pregnancy, and all reactions were negative. None of the infants has ever shown the slightest sign of congenital syphilis. Scurvy supposedly does not appear as early as the age of 1 month, nor were there any clinical signs of scurvy in any of the infants. Almost all of them were breast fed at 1 month. Maxwell described what he believed to be fetal rickets in children born of Chinese mothers during a period of famine. Assuming that the condition he observed actually was fetal rickets, it has been observed only in infants whose mothers have been in a semistarved state for some time. The mothers of the infants whose roentgenograms are described here were, with a few exceptions, on a nearly optimum diet. Rickets acquired after birth could not have been responsible for the rings, since the thirty days from birth to the time these roentgenograms were taken is hardly time enough for active rickets to have developed and healed.

COMMENT

As has already been indicated, the fine white lines just inside the periphery of the tarsal bones (figs. 1 and *2B*) resemble closely and are probably identical with the fine striae often found in the ends of long bones of growing children. Eliot, Souther and Park [4] and others have described such striae in detail and have discussed their formation. They are generally believed to be the result of a temporary cessation or slowing of the rate of invasion into the cartilage of the osteoblastic cells. Such a process is accompanied by a thickening of the temporary zone of calcification in the adjacent cartilage. When invasion of this zone by the osteoblasts is resumed or accelerated, a narrow, heavily mineralized area is left in the shaft of the bone as new bone is formed beyond it. This area appears on the roentgenogram as a white line or

4. Eliot, M. M.; Souther, S. P., and Park, E. A.: Transverse Lines in X-Ray Plates of the Long Bones of Children, Bull. Johns Hopkins Hosp. **41**:364 (Dec.) 1927.

stria. When such striae are seen in roentgenograms of growing children, they are usually interpreted as representing previous periods of decelerated growth (or rickets, since they may result from this condition). Such a variation in growth may result from illness or from any of various causes. Frequently a satisfactory explanation is not apparent.

If the striae found in the tarsal bones at the age of 1 month are of the same nature as the striae found in the ends of long bones, it is desirable to know at what period or age the factors causing the striae occurred. Superimposition of the roentgenograms taken at birth on those taken at 1 month shows that that portion of the total nucleus contained within the stria represents that portion which was present at birth. In other words, the fine white lines at 1 month are identical with the periphery of the nucleus at birth. It was therefore at or very shortly after birth that the slowing of osseous growth occurred, a stria or scar being left which was visible at that point in the later roentgenograms. Striae in the long bones in almost all cases in which tarsal striae appear confirm this belief.

The thickened temporary zones of calcification shown in figures *2 A* and 3 appear to be entirely comparable to the thickened temporary zones at the ends of the long bones. Like those at the ends of long bones, they frequently leave, when they disappear, a fine white line or stria. Many of the tarsal bones showing a thickened temporary zone at 1 month show in the 3 month roentgenograms the same fine white lines demonstrated in figures 1 and *2 B*. The thickened temporary zone of calcification seems to be an intermediary process in the formation of tarsal striae, just as thickened temporary zones in long bones are intermediary processes in the formation of striae of the long bones. As in long bones, there may be thickening of the temporary zone without formation of striae, however. Perhaps because of the severity or prolongation of the metabolic disturbance which produces the thickening of the temporary zone, this zone has not at 1 month resolved into the thin white line within the bony substance, and it is not until later that the line may be apparent in roentgenograms. Those infants showing thickened temporary zones of calcification in the tarsal bones at 1 month also have in most instances shown striae in the ends of some of the long bones at the same age. Figure 5 shows diagrammatically the appearance of the temporary zone at 1 month and the resolution of this zone into the tarsal stria seen at 3 months.

As has been indicated, the small inner or central nuclei shown in figures 4 and 5 when present are always visible in the roentgenograms taken at birth. They appear to have been formed by the seventh month of gestation. They tend to fade rather rapidly after birth, so that at

1 month, while in few cases the nucleus has remained solid or has only a small area of less density in the center, in most cases the nucleus has disappeared except for a ringlike line marking its outer border, and many of the nuclei have disappeared entirely.

To review briefly the differences in the three phenomena described: The white line found at the age of 1 month is from 1 to 2 mm. from the periphery; it is never present at birth, nor is there anything in the roentgenograms taken at birth to suggest that it will appear at 1 month. The band which forms the periphery of the bone at 1 month is never present at birth, nor is there anything at birth to suggest that it will appear. The dense central nucleus when present is always found at birth; it is central instead of peripheral. While at birth it may show some slight tendency to fading or involution in its center, this fading has usually progressed to such a point at 1 month that only its rim, a poorly defined band, is left. In some instances this process has progressed so far at 1 month as to leave only a faint trace of the periphery of the nucleus, which appears as a dotted line. This faint line is discernible in the central portion of the nucleus shown in figure 1 *B*, far inside the large white line.

POSSIBLE FACTORS IN THE PRODUCTION OF RINGS, BANDS AND INNER NUCLEI

Since the striae and the thickened temporary zones of calcification are merely different phases of the same process, their possible causes may be considered as the same. If the phenomena result from interruption of growth as do striae in long bones, one must look for the cause of that interruption at birth, as I have already explained. There are a number of possible factors at that time. The first of these is the shock of birth itself. It seems probable that passage of the fetal head through the birth canal, with pressure due to molding of the cranial bones, produces a marked upset in the metabolic processes of the infant, so that its growth for a short period is materially slowed. The loss in weight of the newborn child may be caused in part by disturbances of metabolic processes incident to the shock of birth, as well as by the changes due to the shift from the maternal blood supply, as a source of fluids and nutriment, to the infant's own gastrointestinal tract. The neonatal loss of fluid and the assumption of function by the gastrointestinal tract may be the principal factors in the interruption of growth which immediately follows birth. Reliable data are not available which might show the degree of interruption of growth in bones during the first week or ten days of life. A third factor which might be of importance in the production of the growth rings is the endocrine readjustment which probably occurs at birth, when the mother's endocrine system

ceases to be a factor in the endocrine balance of the infant. Up to birth, the fetal endocrine balance is probably represented by a combination of the products of the fetal endocrine system and of the endocrine products circulating in the mother's blood. The sudden disturbance of this balance by the elimination of the mother's system as a source of hormones should occasion a fetal readjustment perhaps severe enough to influence growth for a time.

All of these factors would of course be operative to some extent in all newborn infants. One might therefore expect to find changes in growth severe enough to produce tarsal rings in all infants. The fact that I have not found them in some cases does not mean that no osseous change has occurred after birth in those cases. It means only that that change has not been severe enough to be detectable by roentgen examination. The wide variation in the intensity of the phenomena I have seen suggests that such may be the case. In a few of the cases of thickened temporary zones of calcification it was difficult to decide whether the bones were to be classified in the group illustrated in figure 3 or in the uninvolved group. It must be remembered that both the severity of the birth process and the infants' ability to withstand it may differ greatly from infant to infant. After labor of the same duration and apparently of the same severity, two infants whose mothers have comparable pelvic measurements and whose size and birth conditions are apparently similar may with the same postnatal care have quite different neonatal losses of weight. Nevertheless, one may presume that some shock and some physiologic readjustment must occur in every case.

As regards the small central nuclei found prenatally (figures 4 and 5), it is hazardous to attempt a guess as to their cause. It was believed at first that the central nucleus was probably not an area of increased density in the bone, but was rather an irregularity in the shape of the bone which gave the appearance of a denser central portion when viewed on a lateral roentgenogram. However, pictures of the tarsal bones in other positions failed to show any such irregularity. Whether changes in the mineral demands of the fetus as it becomes larger, maternal endocrine or nutritional changes or other unthought of possibilities are responsible is problematic.

SUMMARY

Lines of striae giving the appearance of thin white rings in lateral roentgenograms are found frequently in the tarsal bones of infants at the age of 1 month. Their location and the fact that they are never present at birth indicate that the incident which incited their formation must have occurred at or immediately after birth. Bands forming the periphery of tarsal bones and apparently representing thickened tem-

porary zones of calcification have been observed at 1 month but not at birth. These bands represent a transitional stage in the formation of the striae, although they do not always leave striae when they disappear. Inner, more dense nuclei apparently formed some weeks previous to birth have been observed in the tarsal bones of newborn infants. They tend to fade, beginning in the center, and disappear entirely in two months or less.

I suggest that the first two phenomena described, which are not present at birth, may be the effects of a slowing or cessation of growth at birth, perhaps resulting from the shock of birth itself or from the chemical readjustments that occur in the first few days of postnatal life. The inner nuclei present at birth may well represent a change in growth or a shift in the supply of minerals or hormones which pass into the fetal circulation through the placenta.

NOTE.—This is the first of two papers dealing with evidences of prenatal or neonatal disturbances in growth. In the second I shall report an attempt (by studying the history, physical findings and chemical changes of the mother during pregnancy, the nature of the birth itself and the progress of the infant during its first month of life) to determine whether causes for the osseous phenomena are apparent in individual cases.

PROTECTION PHENOMENON IN MEASLES

DEBRÉ PHENOMENON OR AUSSPARPHÄNOMEN

WILLIAM R. PHILLIPS, M.D.

ELMIRA, N. Y.

The value of the use of convalescent serum or of serum from immune adults for the prevention or modification of measles in exposed susceptible persons has been recognized for nearly twenty years. Placental extract and globulin fractions obtained from placental extract have been used for the same purpose. Attempts have been made to prepare measles antiserum by injecting into animals measles virus or organisms thought to be the specific cause of measles. In addition, the antibodies in the blood of immune adults have been "reactivated" by the introduction of measles virus through various channels, thus enhancing the protective power of the serum of these adults.

It is unfortunate that no accurate methods have been devised for measuring the presence and concentration of measles antibodies, as is possible with many other types of antiserum. It is, perhaps, largely because of this fact that there is such a wide diversity of opinion concerning the efficacy of various products which are used to provide passive immunity to measles.

In 1923, Debré and his co-workers [1] first described local inhibition of the rash of measles by the subcutaneous injection of measles convalescent serum in patients early in the course of the disease. They found that if 1 to 5 cc. of convalescent serum was injected subcutaneously into a patient with measles at the beginning of the period of invasion, an area about the site of injection would remain free from rash. The serum of healthy adults or serum from patients convalescing from diseases other than measles failed to inhibit the eruption. In 1925 Moro and Keller,[2] independently of Debré and his associates, described the same phenomenon; they called it the *Aussparphänomen*.

A study of this phenomenon was undertaken in the hope that it might afford a method for determining the relative potency of serum used in the prevention of measles.

Fifty patients in the preeruptive phase of measles were admitted to the Willard Parker Hospital during the time in which this study was made. Samples of convalescent serum used in this experiment were taken from patients nine to twelve days after the appearance of the

1. Debré, R.; Bonnet, H., and Broca, R.: Compt. rend. Soc. de biol. **89**:70, 1923.

2. Keller, W., and Moro, E.: Klin. Wchnschr. **4**:1719, 1925.

measles rash. To produce the phenomenon, 1 cc. of serum was injected intracutaneously in nearly all cases. More than this amount is not necessary, and less would probably be satisfactory. The skin of the anterior aspect of the chest proved to be the most satisfactory site for the injection.

In 20 of the 50 patients the phenomenon was not produced. In some patients the rash was too scattered or too mild for the phenomenon to be discernible, while in others the rash appeared too soon after the injections were made. It was found that satisfactory inhibition could be obtained in no case in which the rash appeared within thirty-six hours after the injections were made. Whether the antibodies contained in the serum must first have time to become "fixed," or whether irreparable damage has already been done to the tissues within thirty-six hours, is a matter for conjecture. The phenomenon was demonstrated in 115 areas on 30 patients.

In every case in which convalescent serum was injected more than thirty-six hours before the appearance of a satisfactory rash, there remained about the site of injection a clearly defined area which remained entirely free from rash throughout the course of the disease. The diameter of this area varied from 2 to 5 cm. in cases in which intracutaneous injections of 1 cc. were used. When duplicate injections were given to the same patient the areas were of the same size (fig. 1). However, the same serum when given to different patients produced areas of different sizes, depending on the time of the injections with reference to the appearance of the rash and perhaps on other factors.

In cases in which the rash was inhibited by the use of convalescent serum, simultaneous injections of nonimmune human serum, horse serum (scarlet fever antitoxin) and physiologic solution of sodium chloride did not provide local protection. Serum A was collected from a patient at the onset of measles, and serum B was collected from the same patient during convalescence. Serums A and B were then injected simultaneously into a patient in the preeruptive stage of measles. When the rash appeared, four days later, it was found that it invaded the skin over the site of the injection of serum A, while about the site of injection of serum B there was a clearly defined area free from rash (fig. 1).

Solutions of convalescent serum in 0.9 per cent solution of sodium chloride were made in the following concentrations: 25 per cent, 10 per cent, 5 per cent and 2 per cent. It was found that injections of 1 cc. of these solutions, even down to 2 per cent concentration produced the phenomenon. Two per cent solutions of three different samples of serum resulted in areas about 2 cm. in diameter about the site of injection which remained free from rash. When injections of 1 cc. of several dilutions of the same serum were given to a patient, the size of

the areas varied with the concentration, that is, with the amount of protective serum introduced (fig. 2). In some cases the 2 per cent solution was not effective, and the 5 or 10 per cent solution was the most dilute to produce the phenomenon. Here, again, the factor of time seemed important, because the earlier during the period of invasion the serum is administered the more dilute may be the effective solution.

The production of the phenomenon with such dilute solutions had not been expected. The protective power of the serum of an adult who has had measles in childhood is generally regarded to be about one-third or one-fourth that of convalescent serum; therefore, one would expect

Fig. 1.—Sites of injection marked by spots of gentian violet. *A* indicates site of injection of serum taken at onset of illness; *B*, site of injection of serum taken from the same patient after convalescence; *C*, site of injection of serum taken from a second patient during convalescence.

the serum of an adult who has had measles in childhood to produce the *Aussparphänomen* at least as well as does convalescent serum diluted 1:4, assuming that the rash-inhibiting power of a serum is equal to its measles-preventing power. Yet Debré obtained no inhibition with the serum of healthy adults. Using the serum of 5 adults, Moro found some local inhibition of the measles rash with two of the five samples. It was not stated by either of these authors whether or not these adults had ever had measles. In 1931 Baar [3] gave an unstated number of immune adults injections of blood from patients in the invasion period of measles. The fact that serum taken later from these adults would produce the protection phenomenon was considered proof that the

3. Baar, H.: Klin. Wchnschr. **10**:1301, 1931.

measles antibodies in these adults had been reactivated. Apparently no attempt was made to produce the phenomenon with the serum of these adults taken before they had been given blood from patients with measles.

Because of the results obtained with the weak dilutions of convalescent serum, blood was collected from 5 adults who gave a history of measles in childhood. This serum was pooled, and various dilutions were made. The phenomenon was produced with this serum in some cases with solutions as weak as 5 per cent. However, it was not as efficient as convalescent serum when equal quantities of solutions of

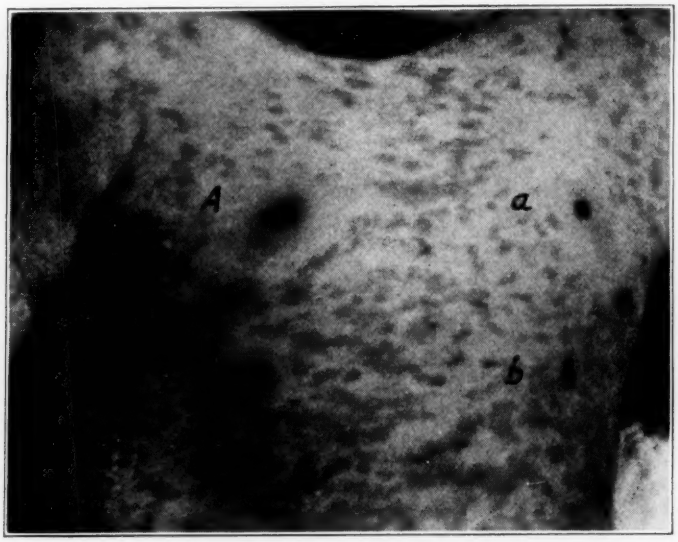

Fig. 2.—*A* indicates site of injection of 10 per cent solution of convalescent serum; *B*, site of injection of 2 per cent solution of convalescent serum; *a*, site of injection of 10 per cent solution of placental extract; *b*, site of injection of 2 per cent solution of placental extract.

equal concentrations were injected simultaneously into the same patient. This relative inefficiency is roughly shown by the smaller sizes of the inhibited areas.

Dilutions were made of derivatives of placental extract. These also would produce the phenomenon but corresponded in efficiency to serum from immune adults (fig. 2).

Much more work is necessary before the results of this or any similar procedure can be accurately evaluated. With the material available in large cities during periods of epidemic, it is probable that this phenomenon could be used to increase the knowledge concerning the prophylactic efficiency of certain preparations.

611 West Water Street.

POLIOMYELITIS ANTISERUM OBTAINED FROM HORSES

II. NEUTRALIZING EFFECT AGAINST VARIOUS STRAINS OF VIRUS

JOHN A. TOOMEY, M.D.
CLEVELAND

Two types of an experimental antiserum have been obtained from horses: one produced by injecting pure eluted poliomyelitis virus as the antigen and the other by injecting pure eluted virus fortified by the addition of enteric toxins and organisms.[1] The fortified antigen produced a better neutralizing serum (1:800 to 1:1,000) than did the plain virus (1:200 to 1:250) against Flexner's M. V. strain.

Since it has been stated that two or three strains of poliomyelitis virus exist, it is obvious that to be of any practical value an antiserum should have some neutralizing value against each strain.

Serums described previously[1] were tested against other strains. These serums (*3732* and *3757*) were obtained from a horse which had been inoculated with fortified antigen and from one that had been inoculated with plain virus antigen. The serums were obtained between May and September 1936, and from eight to twelve months elapsed before they were tested against some of the strains to be described. This is mentioned because with age there is usually a loss of antigenic substance in any serum. However, since only comparative differences were sought, the interval between the withdrawal of the serum and the neutralization tests was an unimportant factor.

Six strains of virus were tested. The results with Flexner's M. V. strain are noted in the first paragraph. Strains of virus labeled Australian, Kramer and Trask weak were obtained from Kramer,[2] and virus labeled Flexner weak and Trask W. E. (or Witte) were obtained from Trask.[3] It was later found that Trask W. E. and Trask weak were the same strains, though carried by different experimenters.

This work was made possible through a grant from Parke, Davis Co., Detroit.

From the Department of Pediatrics, Western Reserve University, and the Division of Contagious Diseases, City Hospital.

1. Toomey, J. A.: Poliomyelitis Antiserum Obtained from Horses, Am. J. Dis. Child. **53**:1492 (June) 1937.

2. Dr. S. D. Kramer, of the Infantile Paralysis Commission, Long Island College of Medicine.

3. Dr. J. D. Trask, of the Yale University School of Medicine.

In any neutralization test the minimal disease-producing dose is always the optimal one for experimentation, but after working with poliomyelitis virus one will soon be convinced that such doses are never entirely standardized and that all experiments with poliomyelitis virus are carried on with only relative doses, i. e., with mere approximations of the minimal paralyzing dose. There was a decided difference in the approximately minimal disease-producing dose and in the type of disease produced with each virus. Two tenths of a cubic centimeter of a 1 per cent suspension of Kramer virus was extremely virulent, regularly producing paraplegia or quadriplegia within from seven to ten days; in this respect it was similar to Flexner's M. V. strain. Two tenths of a cubic centimeter of a 2 per cent suspension of Trask W. E. virus could be said to occupy a middle position as to virulence between the Kramer and the Australian strain. Two tenths of a cubic centimeter of a 10 per cent suspension of Trask W. E. virus produced quadriplegia within from seven to ten days; 0.1 cc. of a 2 per cent suspension produced paresis of both legs within from six to twelve days. A 0.1 cc. dose of a 2 per cent suspension of Australian strain never produced more than paresis or paralysis of the legs. Trask weak virus and Flexner weak virus were alike in that neither produced much paralysis; weakness or paresis of muscles usually resulted, even though 10 per cent virus suspensions were used. These weaknesses came on from six to eleven days after intracerebral injection. Thus it is obvious that there is no comparison between the virulence of a 10 per cent suspension of the Flexner weak strain and that of a 10 per cent suspension of the Flexner M. V. strain. Although there is a difference, there is no reason to believe that it is any more than quantitative.

The serums to be tested were added to equal quantities of virus suspensions and, together with control virus suspensions, were incubated for two hours. One tenth of a cubic centimeter of the mixture of virus and antiserum was then injected intracerebrally into Macacus rhesus moneys. The same virus suspension was used for the same set of neutralizing antibodies and for the controls. The material for each test was made up on the same day. The only unknown factor in any experiment was the serum.

The details and results are outlined in the accompanying table. It can be seen that serum 3732 (fortified) neutralized 2 per cent suspensions of Australian virus somewhere between a 1:100 and a 1:400 final dilution, whereas a 1:20 dilution of serum 3757 did not neutralize. In the control animals paresis or paralysis of the legs developed from six to ten days after the injection of virus.

Trask W. E. virus was neutralized by serum 3732 between a 1:50 and a 1:100 dilution, while serum 3757 failed to neutralize, even in a 1:10 dilution. All control animals manifested the disease from six

*Neutralizing Reaction of Fortified and Unfortified Purified Antigen Serum (Horse)**

Virus	Percentage Used	Fortified Serum 3732 Neutralized Against					Unfortified Serum 3757 Neutralized Against					Controls		
		Monkey No.	Serum	Result	Days	Final Dilution	Monkey No.	Serum	Result	Days	Final Dilution	Monkey No.	Result	Days
Australian (Kramer).....	5	1101	1/500	±	33	1,000	1102	1/500	+	17	1,000	1103	+	7
												944	+	9
Australian (Kramer).....	5	1126	1/200	+	11	400	1127	1/200	+	11	400	1128	+	6
Australian (Kramer).....	2	1168	1/50	—	..	100	1169	1/50	+	9	100	1170	+	10
Australian (Kramer).....	2	1194	1/25	—	..	50	1195	1/10	±	7	20	1196	+	7
Trask W. E. (Trask).....	10	961	1/5	±	..	10	962	1/5	+	6	10	942	+	7
Trask W. E. (Trask).....	2	998	1/50	+	17	100	999	1/50	+	10	100	1100	+	10
Trask W. E. (Trask).....	2	1123	1/50	±	11	100	1124	1/25	+	6	50	1125	+	6
Trask W. E. (Trask).....	2	1174	1/25	—	..	50	1175	1/10	+	12	20	1153	+	12
Trask W. E. (Trask).....	2	1197	1/10	—	..	20	1198	1/5	+	10	10	1199	+	11
Kramer (Kramer).....	10	959	1/5	—	..	10	960	1/5	+	7	10	941	+	7
Kramer (Kramer).....	2	995	1/500	Died of worms		1,000	996	1/500	+	7	1,000	997	+	7
Kramer (Kramer).....	2	1120	1/500	+	10	1,000	1121	1/500	+	6	1,000	1122	+	6
Kramer (Kramer).....	2	1171	1/150	—	..	300	1172	1/75	+	10	150	1173	+	11
Kramer (Kramer).....	2	1300	1/50	—	..	100	1301	1/10	±	10	20	1302	+ plus worms	6
Trask weak.....	10	1129	1/500	±	12	1,000	1130	1/500	+	10	1,000	1131	+ plus worms	11
												945	+	9
Trask weak.....	10	....	.....	..	..	.....	1157	1/100	—	..	200	1158	+	11
Trask weak.....	10	1303	1/100	—	..	200	1304	1/50	— (?)	..	100	1305	+ plus worms	6
Flexner weak.....	10	1132	1/500	—	..	1,000	1133	1/500	+	10	1,000	1134	+	10
												943	+	10
Flexner weak.....	10	....	.....	..	..	.....	1159	1/100	±	11	200	1160	+	9
Flexner weak.....	10	1306	1/100	—	..	200	1307	1/5	±	10	10	1308	+	6

* + indicates paralysis; —, no paralysis; ±, weakness of muscles.

to twelve days after intracerebral injection. The condition which developed in the controls depended in some measure on the dose, as can be seen from the table.

The virulence of a 2 per cent suspension of Kramer virus was similar to that of Flexner's M. V. strain; it was neutralized somewhere between a 1:300 and a 1:1,000 dilution. Serum *3757* was unable to neutralize, even in a 1:10 dilution. In all controls the disease developed from six to eleven days after injection, and all had quadriplegia.

A 10 per cent suspension of Trask weak virus was easily neutralized by both serum *3732* and serum *3757* in rather high dilutions. The controls, although results were positive, merely had paresis.

A 10 per cent suspension of Flexner weak virus was neutralized by serum *3732* in a dilution as high as 1:1,000. Serum *3757* gave some protection at 1:200. The control animals, like those inoculated with Trask weak virus, showed only paresis of muscles.

COMMENT

The virus used to produce the antiserum in these experiments was Flexner's M. V. strain. The horses immunized were inoculated on the same day with equal amounts of the same antigen virus suspension, which had been made on the same day. There was only one difference: the addition of enteric organisms, endotoxins and exotoxins to one antigen mixture, which resulted in the so-called fortified antigen.

Notwithstanding the fact that the additional stimulus was theoretically nonspecific, it is obvious that these nonspecific factors when added to the virus so enhanced the production of antiviral substances in the inoculated animal that antiserums produced in this manner had a neutralizing effect on other, so-called heterologous, virus strains. Not only was this true, but fortified antigen serum had better neutralizing antibodies against the homologous strain.

Such results make one wonder whether the products of the metabolism of the gastrointestinal tract are wholly to be ignored. In themselves, such toxic products do not produce poliomyelitis, but when added to the naked virus they may synergize and accelerate the destructive action of the virus. If such combinations are injected intracerebrally in sufficient amounts, they may produce signs of immediate hemiplegic involvement. Now it has been found that these combinations produce better antibodies than the virus alone. This antigen also produced paralysis in the horse. The mere fact that enteric products enhance the value of virus antigen favors the belief that the metabolic products of the gastrointestinal tract may play some role in this disease.

It is important to know whether virus strains exist which have qualitative differences. In none of my other experiments could it

be certain that there were more than quantitative differences in strains. Curiously enough, the strains themselves gave some evidence of quantitative differences. Trask W. E. strain, obtained from Trask, was fairly virulent and produced quadriplegia in animals inoculated intracerebrally if the dose was large enough. A specimen of the same virus, received from Kramer (Trask weak or Witte), did not produce quadriplegia but resulted only in paresis of muscles, no matter what dose was injected. The virus strains were supposedly identical, though each was carried by a different experimenter; yet the neutralizing reactions of the antiserums against the strains were markedly different. Purified eluted Flexner M. V. antigen antiserum neutralized a 10 per cent suspension of Trask weak virus (obtained from Kramer) from a 1:200 to 1:1,000 dilution, while the same antiserum failed to neutralize Trask W. E., obtained from Trask, in a 1:10 dilution.

In other experiments [4] it was determined that if quadriplegia was produced in Macacus rhesus monkeys by a strong strain injected intracerebrally, the animals were practically immune to subsequent injections of that or any other strain of virus, provided the subsequent doses were only equal in virulent strength to the doses which originally produced the disease. However, an animal might again contract quadriplegia if massive multiple doses of the original homologous or heterologous virus were injected after it had recovered from a generalized attack.

If a weak strain of virus was intracerebrally injected in monkeys, the disease which followed might be mild in character, and the immunity acquired by the animals might be sufficient to protect them against equal doses of the same or of another strain of weak virus. On the other hand, animals that had recovered from a mild form of the disease practically always contracted it again with an ordinary dose of a strong virus, and the disease invariably recurred if the dose of the homologous or heterologous virus contained a great number of multiple units of the disease-producing dose.

The apparent difference in strains could easily be explained if these differences were quantitative in character. It could then be stated that the antigen antibody response depended on the relative quantitative virus content of the antigen. Thus the higher the virus content in the antigen, the greater would be the stimulus, the higher would be the neutralizing antibody titer produced and the greater would be the resulting immunity in the inoculated animal.

4. Toomey, J. A.: Second Attacks of Poliomyelitis in Macacus Rhesus Monkeys, Am. J. Dis. Child. **52**:802 (Oct.) 1936.

CONCLUSIONS

A fortified antigen, as previously reported,[1] produces an antiserum which has neutralizing antibodies against several strains of poliomyelitis virus. When unfortified virus is used as an antigen, the neutralizing antibody reponse is not so potent against the stronger strains, and is not quite, but nearly, as strong against the weaker strains. The neutralizing character of the antiserum may be quantitative. The antiserum described is merely experimental and was used only in Macacus rhesus monkeys.

Case Reports

PULMONARY ECHINOCOCCOSIS

CHARLES J. LESLIE, M.D.
NEW YORK

Infestation by Echinococcus granulosus is uncommon in the United States. The discovery of primary bilateral pulmonary hydatid cysts in a child of 7 years is so rare as to be a clinical curiosity.

Osler,[1] in 1882, made the first collection of cases of hydatid disease in North America. Using case records, museum specimens and personal communications from the United States and Canada, he was able to find 61 cases, in 5 of which the lesions were pulmonary. In 1895, Sommer[2] increased the number of recorded cases to 110. Lyon's[3] series (1902) further increased the number of reported cases to 241, in 11 of which pulmonary cysts were noted. Magath[4] (1921) collected 68 cases more from the literature and added 25 from the records of the Mayo Clinic, bringing the total to 334 cases. In 5 of Magath's collected cases there were cysts of the lung; thus the total number of recorded instances of pulmonary lesions was 21 up to 1921. Phillips[5] in 1930 collected 34 cases of pulmonary hydatids from the literature and added 2 cases of his own, bringing the total number of recorded cases to 36 (10.7 per cent). In the group collected by Phillips, there were only 6 cases in which multiple lesions in the lungs were conclusively diagnosed.

The relative incidence of pulmonary cysts in this country is comparable with the incidence in localities where the parasite is more common, though the absolute number is much smaller here. Greenway[6]

From the Department of Pediatrics, New York Post-Graduate Medical School and Hospital of Columbia University.

1. Osler, W.: Echinococcus Disease in America, Am. J. M. Sc. **84**:475, 1882.

2. Sommer, H. O.: Echinococcus Disease in the United States, New York M. J. **62**:656, 1895; **64**:263, 1896.

3. Lyon, I. P.: A Review of Echinococcus Disease in America, Am. J. M. Sc. **123**:124, 1902.

4. Magath, T. B.: Echinococcus Disease: Etiology and Laboratory Aids to Diagnosis, M. Clin. North America **5**:549, 1921.

5. Phillips, E. W.: Hydatid Cysts of the Lung, Arch. Surg. **21**:1324 (Dec.) 1930.

6. Greenway, D. J., cited in Echinococcus Disease, Foreign Letters, J. A. M. A. **79**:2019 (Dec. 9) 1922.

noted an incidence of 14.7 per cent of pulmonary lesions in Buenos Aires, Argentina, in a collection of 2,740 cases of echinococcosis. Lavillat [7] found cysts of the lungs in 15.7 per cent of 210 cases. Vegas and Cranwell [8] reported an 8.5 per cent incidence of pulmonary hydatids. Vegas,[9] as he reported in his extensive monograph on pulmonary hydatid cysts in children (1928), found 74 instances of the condition in a total of 560 cases, an incidence of 13.2 per cent. In only 3 of these cases were there cysts in both lungs.

Although most authorities have agreed that the infestation probably occurs in early life, it is not common to find the cysts at this period. Vegas reported the following age incidence in 50 cases:

Age, Yr.	No. of Cases
1- 5	5
6-10	19
11-15	25
Not specified	1

The youngest patient cited in Phillips' report of North American cases was 17 years old.

REPORT OF A CASE

A 7 year old American-born boy of Italian descent was admitted to the New York Post-Graduate Medical School and Hospital on July 31, 1935, with a complaint of recurrent attacks of fever, with a temperature as high as 105 F., for three weeks. The symptoms came on suddenly after an automobile ride. With the fever he had a slight nonproductive cough, mild night sweats and some loss of weight, but no hemoptysis. At the onset of the symptoms he was confined to bed because of weakness, but he was up and about for one week before his admission. Five months before this he was ill with pneumonia for two months.

Previous illnesses included mild pertussis and chickenpox. He was one of 4 children. His birth was normal and the family history was irrelevant.

On admission he was well nourished and did not appear acutely ill. The temperature was normal. The positive physical findings included cryptic tonsils and marked dental caries. There was dulness over the left posterior part of the chest, with flatness at the base of the left lung. Fremitus and voice sounds were diminished, and breath sounds were absent over the base of the left lung and in the left axilla. There was slight dulness over a small area in the right axilla, with some questionable diminution of breath sounds. The heart was slightly displaced to the right. The physical examination otherwise gave normal findings.

Laboratory tests gave the following findings: The urine was normal. The Wassermann test of the blood was negative. The Mantoux test (with a dilution of 1:1,000) was negative. The red blood cells numbered 4,000,000, and the

7. Lavillat, F.: Hydatid Cysts of the Lung, Internat. Clin. **2**:47, 1922.

8. Vegas, M. H., and Cranwell, D. J.: Hydatid Cysts, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1920, vol. 2, p. 434.

9. Vegas, M. H.: Hydatid Cysts of the Lung in Children, Buenos Aires, S. A. Imprenta & Cia, 1928.

hemoglobin content was 11 Gm. per hundred cubic centimeters. The white blood cells numbered 12,000; 57 per cent were polymorphonuclears, 39 per cent were lymphocytes and 4 per cent were eosinophils. A roentgenogram of the lungs (August 2) showed a large circumscribed area of density, apparently due to encapsulated fluid, in the lower lobe of the left lung (fig. 1 *A*). In the lower lobe of the right lung was an area of density about 2.5 cm. in diameter (fig. 1 *B*).

The preliminary impression was that the patient had an encapsulated empyema.

Thoracentesis was done, and clear watery fluid under slight pressure was found. Analysis of this showed a specific gravity of 1.006, a protein content of 0.02 per cent, no cells and no globulin. Because of the peculiar nature of the fluid an echinococcus cyst was suspected. A search was made for hooklets in the fluid, but none was found. An intradermal injection of 0.2 cc. of the fluid produced a slight reaction, which persisted for twenty-four hours.

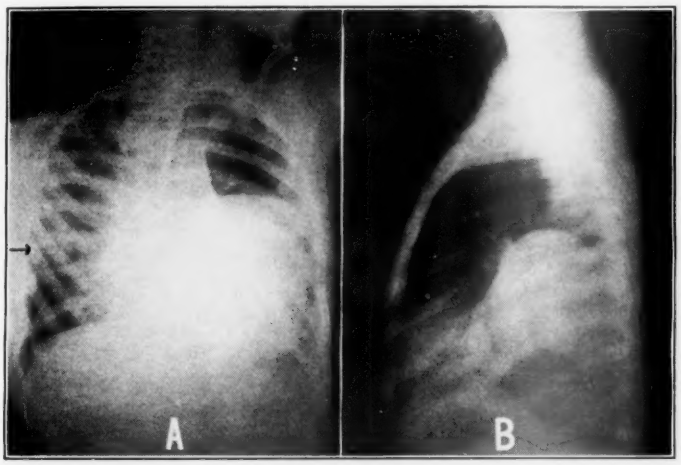

Fig. 1.—Roentgenograms of the lungs taken Aug. 2, 1935. *A* and *B*, two views of the large circumscribed area of density, apparently due to encapsulated fluid, in the left lower lobe and the area of density, about 2.5 cm. in diameter, in the right lower lobe.

At this point the history was reinvestigated. It was found that two years previously the boy spent some time on a farm in Italy, and that while there he had a pet dog.

A complement fixation test for the echinococcus was done in the laboratories of the New York Post-Graduate Medical School and Hospital, the New York Presbyterian Hospital and the United States Bureau of Public Health. The results were all strongly positive. An intradermal test with 0.1 cc. of echinococcus antigen caused an immediate wheal formation. The eosinophil count, which was taken on several occasions, varied from 4 per cent to 21 per cent.

Because of these findings a diagnosis of bilateral echinococcus cysts of the lung was considered to be fairly certain.

After the thoracentesis there developed a violent pleural reaction, with toxicity, a temperature of 103 F., pain and a friction rub. In addition there was clinical

evidence of pneumothorax. A roentgenogram taken at this time (fig. 2) showed a large thick-walled cyst in the parenchyma of the left lung, with hydropneumothorax on the left side. The cyst contained only a small amount of fluid. Apparently the contents had escaped into the pleural cavity.

This resulted in much toxicity, a high temperature and meningismus. All these cleared up within a few days, and the pleural exudate was absorbed. Pneumothorax, however, progressed and caused such mediastinal displacement that decompression had to be done (fig. 3).

Two weeks later a thoracotomy with resection of the eighth rib was done. Removal of the cyst and marsupialization of the cavity were found impracticable,

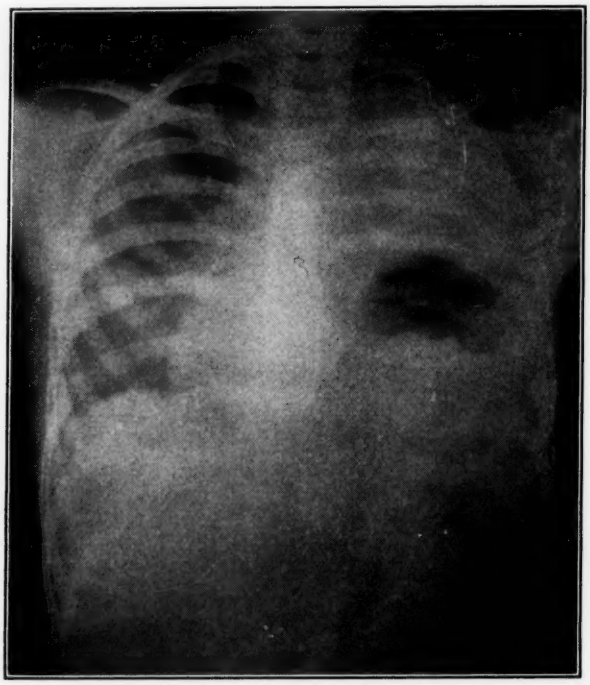

Fig. 2.—Roentgenogram taken after thoracentesis, showing the large, thick-walled cyst in the parenchyma of the left lung and left hydropneumothorax.

and simple drainage by tube was established at the ninth interspace. The patient had a moderately severe febrile postoperative reaction lasting three or four days. The tube was removed on the ninth day.

The child was discharged sixteen days after operation, in fair condition.

The prognosis was considered poor because the cyst had not been removed, because the hydatid fluid (presumably infective) had been disseminated throughout the pleural space and because the nodule in the right lung apparently was another cyst.

A roentgenogram of the lungs (October 23) made five weeks after operation showed reexpansion of the left lung, with definite reduction in the size of the cyst (fig. 4). The cyst in the right lung was perhaps a shade larger than before. The patient's clinical condition at this time was good.

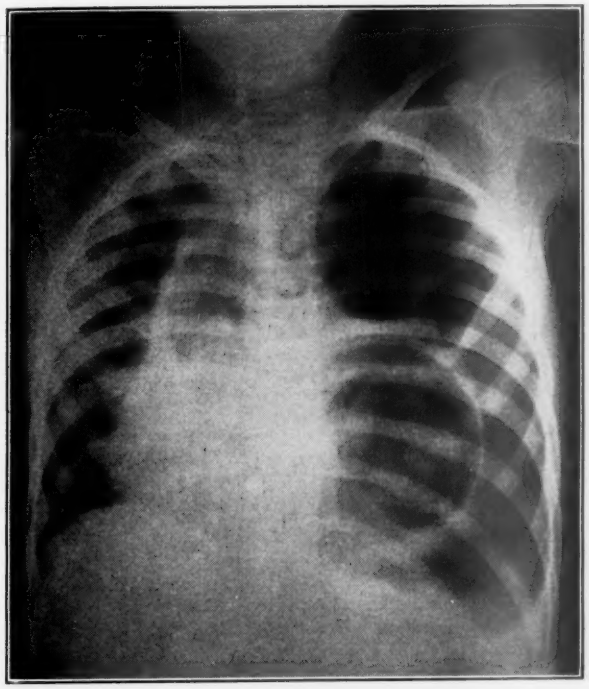

Fig. 3.—Roentgenogram showing progression of pneumothorax and mediastinal displacement.

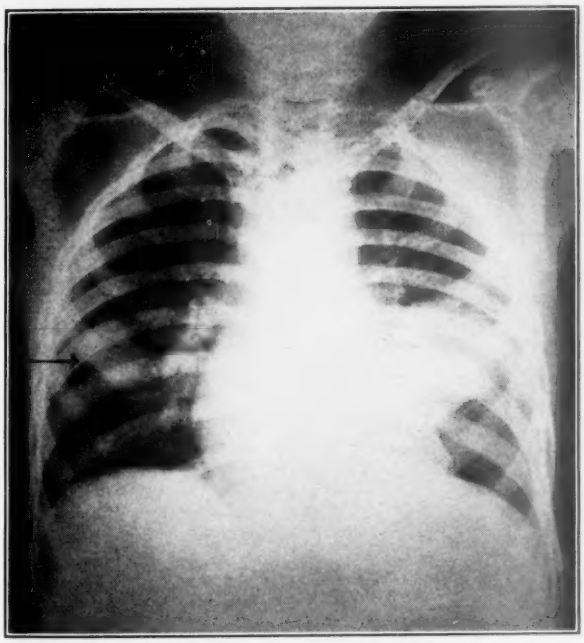

Fig. 4.—Roentgenogram taken on Oct. 3, 1935, five weeks after operation. Reexpansion of the left lung and definite reduction in the size of the cyst on the left are seen. The cyst in the right lung is perhaps a shade larger than before.

He was readmitted to the hospital on Jan. 2, 1936, with a history of abdominal pain and vomiting of two days' duration following ingestion of six or seven glasses of wine. Examination disclosed a temperature of 103 F. and generalized abdominal rigidity and tenderness. A diagnosis of acute appendicitis with perforation and probable generalized peritonitis was made, and an immediate laparotomy was done. A perforated gangrenous appendix was found, with generalized peritonitis. The patient had a stormy course and died fourteen days after operation. Permission for necropsy was refused.

At no time during his illness previous to the appendicitis was there any evidence of a lesion in any organ other than the lungs. It is unfortunate that necropsy was not permitted. Nevertheless, the diagnosis seems to have been soundly established.

COMMENT

This case presents interesting features other than the rarity of the condition. In retrospect, it appears that the correct diagnosis should have been made, or at least suspected, before thoracentesis was performed. Certainly empyema was suggested on the patient's admission by the history of spiking fever, cough and sweats following a reported pneumonia, and by the physical signs of fluid at the base of one lung. However, too little attention was paid to the obscure physical signs in the other lung. The roentgen picture of circumscribed spherical density in the parenchyma of each lung should have suggested the diagnosis. Had the condition been suspected, thoracentesis would certainly not have been done before the specific serologic tests had been employed. All authorities have deplored this operative procedure because of the danger of disseminating scolices and of causing severe anaphylactic shock. This patient had a severe toxic reaction after aspiration, although the fluid was apparently sterile. Vegas pointed out the rarity of secondary implantation following the rupture of pulmonary cysts, although this occasionally does occur. Because of technical difficulty, complete removal of the cyst with marsupialization of the cavity was not carried out; yet the result of simple drainage seemed to be promising.

As for the recognition of future cases, the diagnosis apparently will largely depend on correct interpretation of the roentgen picture. The disease is still so rare in this country and its symptoms are so similar to those of other pulmonary conditions that the diagnosis ordinarily will not be made on the usual physical examination.

For a detailed description of the life cycle of the parasite and of the pathology and symptomatology of the disease and for a complete bibliography, the reader is referred to the excellent article of Phillips and to the extensive monograph of Herrera Vegas.

MELORHEOSTOSIS LÉRI

JAMES B. GILLESPIE, M.D.
AND
JOHN A. SIEGLING, M.D.
URBANA, ILL.

In 1922 Léri and Joanny [1] first described a type of pathologic change of the bone for which they proposed the term melorheostosis, or flowing hyperostosis of a limb. The condition, which can be identified roentgenographically, is characterized by a dense cortical hyperostosis causing an enlargement of the affected part and extending in a linear streak along the bones of an extremity into some of the tarsal or carpal bones. In the cases reported, with one exception, the changes were confined to a single extremity, either upper or lower; this localization suggested to Putti [2] the name osteosis eburnisans monomelica.

There is no unanimity of opinion as regards the etiology of the condition. Kraft [3] summarized four theories: It has been ascribed to (1) a vasomotor neurosis in which the flow of blood to the affected part is altered, (2) an infectious process, (3) a constitutional endocrine disturbance and (4) an embryonic defect, such as a metameric disturbance. In addition, Moore and De Lorimier [4] suggested the possibility of congenital or developmental subperiosteal telangiectasis. For the most part these theories are without adequate substantiation.

There are few subjective symptoms, and laboratory studies, other than roentgenography, that have added little to assist in the diagnosis. In general, the disease is of insidious onset; the symptoms become progressively more manifest, leading to examination of the skeletal structures by means of roentgenograms. The paucity of clinical symptoms makes it probable that in many cases in which no roentgenographic studies are

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From the Department of Pediatrics and the Department of Orthopedics, Carle Hospital Clinic.

1. Léri, A., and Joanny: Une affection non décrite des os: Hyperostose "en coulée" sur toute la longeur d'un membre ou "mélorhéostose," Bull. et mém. Soc. méd. d. hôp. de Paris **46**:1141-1145 (July) 1922.

2. Putti, V.: Una nuouva sindrome osteopatica: L'osteosi eburneizzante monomelica, Chir. d. org. di movimento **11**:335-361 (June) 1927.

3. Kraft, E.: The Pathology of Monomelic Flowing Hyperostosis or Melorheostosis, Radiology **20**:47-55 (Jan.) 1933.

4. Moore, J. J., and De Lorimier, A. A.: Melorheostosis Léri, Am. J. Roentgenol. **29**:161-171 (Feb.) 1933.

made this disease remains undiagnosed. A constant feature is the sparing of the joints; only in exceptional cases is ankylosis noted. Kahlstorf[5] stated the opinion that severe functional disturbances occur rarely and only when para-articular periostosis limits the mobility of the affected joint or when the hyperostotic process leads to irregularities in the contours of the joint and thus influences the articular function.

Widmann and Stecher,[6] in an excellent chronological review of the literature published in 1935, summarized the twenty-five reported cases. The ages of the patients varied from 6 to 54 years; sixteen were males and nine were females. Dillehunt and Chuinard[7] in 1936 reported observations on a case of melorheostosis in a 10 year old boy; certain sclerodermic cutaneous changes, however, had been noted in the affected limb when he was 6 months of age. Superimposed on the affected portion of bone and forming the same general pattern was the associated scleroderma.

We report here a case of melorheostosis with associated scleroderma which came under our observation. The case is of unusual interest for a number of reasons. Certain deformities of the toes, persistent flexion of the thigh on the hip and stony induration of the skin at birth prompted roentgen studies of the affected limb when the patient was 1 month of age. In these roentgenograms the skeletal structures of the affected limb, including the joints, appear normal. Most patients have first come under observation in adult life; this patient is one of the two children under 10 years of age who have been studied. Except in the report of Dillehunt and Chuinard, scleroderma associated with melorheostosis has not been mentioned heretofore. The scleroderma in their case became evident when the patient was 6 months of age; in our own case it was congenital. We have been unable to find a report of melorheostosis with or without associated scleroderma in any pediatric literature. Figure 1 shows the shortening of the leg and of the foot and, to some extent, the atrophy. The child was 8 years of age at the time of the photograph. Figures 2 and 3 show the lesions of the bones.

REPORT OF A CASE

A. M., a girl aged 7 years, was first seen at the clinic on July 15, 1936, because of shortening of the right leg. She had been delivered at term, labor had been

5. Kahlstorf, A.: A Contribution to Our Knowledge of Melorheostosis (Léri) and the Generalized Ostitis Condensans or Osteopoililosis (Albers-Schöenberg), Röntgenpraxis **2**:721-732 (Aug.) 1930.

6. Widmann, B., and Stecher, W.: Rhizomonomelorheostosis, Radiology **24**:651-670 (June) 1935.

7. Dillehunt, R., and Chuinard, E.: Melorheostosis Léri, J. Bone & Joint Surg. **18**:991-996 (Oct.) 1936.

induced and delivery was normal. Her weight at birth was 7½ pounds (3,402 Gm.). When 3 days old she became jaundiced, and for about one week her condition was not considered good. The family history was essentially negative.

At birth, deformity of the toes of the right foot was noted. The right thigh was held flexed on the hip; the right leg appeared shorter than the left, and the skin of the lower part of the right leg, of the right thigh and of the right buttock was indurated on all aspects. When the child was 1 month of age, roentgenograms of the right hip were made. The skeletal structures appeared normal at that time. The child's grandfather was a physician, and he followed her development with great interest. She had her first teeth at the age of 6 months, walked at 11 months and talked at 18 months. Her general physical development, except in the affected limb, was normal. The right leg remained shorter than the left, the right foot was

Fig. 1.—Note the shortening of the right leg and foot and the shiny appearance of the skin. Moderate atrophy is present.

smaller than the left, and the induration of the skin persisted. Although she walked with a limp, she enjoyed the sports of other children and took dancing lessons. Since the time when she had first worn shoes a lift for the right sole had been used. The parents said that improvement had occurred in the range of motion of the joints and in the condition of the skin as a result of persistent massage at home.

Physical examination showed a well nourished, cooperative, bright girl. Her height was 45 inches (112.5 cm.) and her weight 45 pounds (20.5 Kg.). The physical examination, except that of the right lower extremity, gave essentially negative findings. There was thickening of the skin and of the subcutaneous tissues; this extended from the anterosuperior iliac spine posteriorly, involving the right buttock. The skin of the entire right thigh and of the lower part of the right leg to the foot was involved. Scleroderma was more marked on the lateral aspects of the leg. There was no complaint on movement of the joints, but a persistent

abduction deformity due to the tightness of the cutaneous structures was present. The shortening of the leg seemed equally divided between the femur and the tibia. A 15 degree flexion deformity of the right knee was present, and passive flexion of the knee was limited to 50 degrees; motion of the ankle was limited on the right. These limitations of motion were due to scleroderma. There was shortening of the bones of the foot, and there was little motion of the fourth and fifth toes. The right leg was 2¼ inches (6 cm.) shorter than the left and showed moderate atrophy. Sweating was apparently normal in the right lower extremity.

Urinalysis and a complete blood count gave normal findings. The Kahn test and a Mantoux test with 0.1 mg. of old tuberculin were negative. The amount of calcium in the blood was 11.9 mg., and that of phosphorus, 5.2 mg., per hundred cubic centimeters. Roentgen examination of the pelvis showed that the bones of the right side were slightly underdeveloped and that the pelvis was tilted on the

Fig. 2.—Roentgenogram of the pelvis, showing the alteration of structure in the right iliac wing and in the upper third of the right femur.

lumbar spine so that the right side was much lower than the left. In the right iliac wing the bone showed considerable alteration of structure: There was loss of the normal trabeculation, and there were alternate areas of osteosclerosis and of rarefaction, extending vertically. The upper branch of the pubic bone was completely sclerosed, while from the ischium an area of greater density extended part way to the symphysis. In the head of the right femur the areas of alternate opacity and rarefaction assumed a radial appearance. In the neck of the femur and in the region extending from the neck to a point well below the trochanteric region the alteration of the bony structure had again a longitudinal appearance. The cortex of the femoral shaft was greatly thickened, especially at the expense of the medullary cavity. In the lower femoral epiphysis, as well as in the upper tibial epiphysis, rounded alternate areas of opacity and of rarefaction were observed. The shaft of the right tibia and that of the fibula showed irregular thickening of the inner side of the cortex. Alterations similar to these were visible in the metatarsal bones and in the phalanges, while the tarsal bones showed a structure

similar to that seen in the lower epiphysis of the femur and in the upper epiphysis of the tibia. The bones of the right lower limb were considerably shorter than those of the left. Roentgen examination of the remaining portions of the skeleton and of the lungs gave negative results.

Studies of the cutaneous temperature showed changes in the right leg comparable to those which occurred in the left after the ingestion of alcohol. A biopsy was not done. The patient was dismissed without treatment, although it was recommended that massage be carried out as before and that she return annually for observation.

She was last seen on Sept. 10, 1937. At that time there seemed to be improvement in the skin of the leg and in the motion of the affected joints. The parents

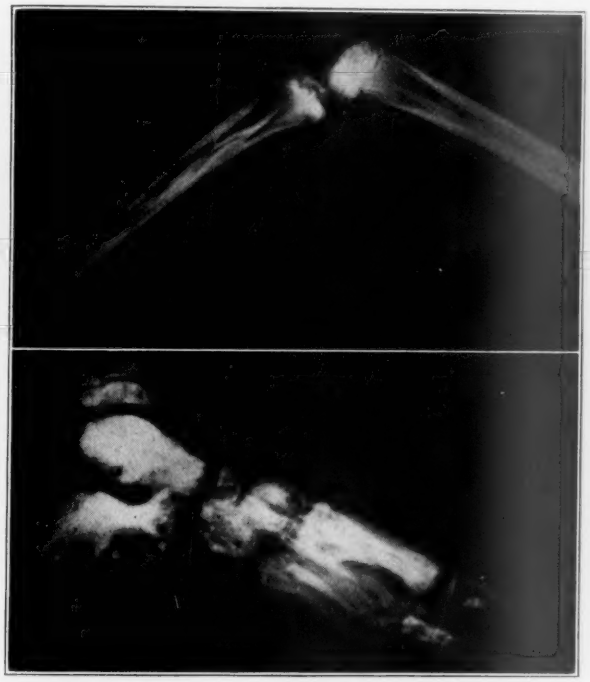

Fig. 3.—The upper roentgenogram shows lesions in the diaphysis of the right femur and of the right tibia. The lower one shows the spongy appearance of the lesions in the short bones of the right foot.

felt definitely that much had been accomplished by massage and by passive motion of the right lower extremity.

COMMENT

The fact that pathologic changes in the bone were not seen in roentgenograms of the affected limb taken when the patient was 1 month of age would tend to invalidate Zimmer's [8] embryonic theory, that meta-

8. Zimmer, P.: Ueber einen Fall einer eigenartigen seltenen Knochenerkrankung, Osteopathia hyperostotica—Mélorhéostose, Beitr. z. klin. Chir. **140**:75-85, 1927.

meric disturbances are the cause of melorheostosis. In previously reported cases there has been no record of negative skeletal findings prior to the appearance of the typical lesions of the bone in later life. Consequently there has been no evidence heretofore that these lesions are not of congenital origin. In the case reported here we cannot estimate the time at which changes first appeared in the bone. The association of congenital scleroderma with melorheostosis is rare, judging from the fact that the case of Dillehunt and Chuinard is the only one similar to ours. In their case the scleroderma was entirely confined to lateral aspects of the extremity; in ours, involvement was more or less general in the affected member. The distribution of the congenital scleroderma in our case suggests that the condition is related to the melorheostosis, which appeared later. There is no suggestion of a hereditary factor.

In studying this case and the reports of others we were not impressed by any symptoms which might be characteristic of a melorheostosis syndrome. The symptoms and physical findings are generally vague and lead sooner or later to roentgen studies. The neurologic or rheumatic complaints reported by some were not found in this case, although there were atrophy of the extremity and a definite limp.

The diagnosis of melorheostosis is made chiefly by means of roentgenograms. The characteristic features are indicated in the name flowing hyperostosis. This abnormality extends along a part or down the full length of the limb and is typically unilateral. Weil and Weismann-Netter [9] reported a case of melorheostosis in which they felt that the right fourth rib was affected in addition to an extremity. For this reason they suggested discarding the term melorheostosis (*melo*, extremity) and substituting the word rheostosis. In all reported cases other than theirs, extremities alone were involved. The lesion is benign and progressive and is endosteal, periosteal or both. In the pure endosteal type no true enlargement of the bone is noted. Junghagen,[10] in commenting on the slow growth of the lesions, explains that sclerosis obeys the same laws as the general ossification of the body, which may be regarded as terminated only in the third decade of life. Typically there are dense linear irregular excrescences extending along one side of the bone and usually missing the joints. The lesions are eburnated, but adjacent portions of bone may be rarefied; occasionally there are circumscribed areas of involvement. Fractures through the lesions have not been reported.

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9. Weil, M., and Weismann-Netter, R.: Un cas de rhéostéose (mélorhéostéose de André Léri et Joanny), Gaz. méd. de France, Jan. 15, 1932, pp. 50-52.

10. Junghagen, S.: Sur la mélorhéostose. J. de radiol. et d'électrol. **14**:495-500 (Sept.) 1930.

Biopsies have been done in five cases, but histologic examination has revealed no characteristic changes. In general, there is a rather constant finding of fibrotic replacement of fat marrow in the medullary canal. No postmortem examinations have been performed, as the general health of these persons is usually good, many of them being little troubled by the condition.

There is no known treatment for melorheostosis per se, and the symptoms are treated symptomatically. Roentgen therapy has been attempted empirically, on the assumption that subperiosteal telangiectasis exists, but no definite regression or improvement has been reported. In our own patient there seemed to be some improvement in the scleroderma under massage carried out over a long period.

SUMMARY

A case of melorheostosis involving the right lower extremity is reported. The fact that no lesions of the bone were seen in roentgenograms taken at the age of 1 month is an observation of etiologic interest. Congenital scleroderma associated with melorheostosis is apparently rare. Shortening of the affected bones and a limp are unusual findings in the disease.

ACUTE PHOSPHORUS POISONING

SIDNEY BLUMENTHAL, M.D.
AND
ARTHUR LESSER, M.D.
NEW YORK

The following case of acute phosphorus poisoning with recovery in an infant presents certain features of interest and is therefore reported at this time.

REPORT OF CASE

F. S., a white American boy, 8 months of age, was admitted to the Mount Sinai Hospital on Oct. 1, 1935. His past history was entirely unimportant. On the previous morning, while at play in the kitchen, the child had come in contact with roach paste containing 1.19 per cent yellow phosphorus, which was spread on a piece of potato. When seen by his parents the child's fingers and lips were covered with paste and some was in his mouth. The father attempted to induce vomiting without success. As the child showed no ill effects at the time, medical aid was not sought. During the day the infant seemed to be in good health and took his feedings well, but early in the evening he appeared listless, drowsy and somewhat feverish. He vomited three times that night (the parents did not notice the odor or any unusual characteristics of the vomitus). The following morning, as the child's condition seemed much worse, he was hospitalized.

Examination.—On examination at the time of admission pallor was extreme. The infant was apathetic but could be aroused. He apparently was not able to recognize his parents. The skin was cold and moist. The pulse was rapid (rate, 120) and of poor quality; the temperature was 102.4, and the respiratory rate was 44. The liver was enlarged, its lower border reaching 4 cm. below the costal margin in the right nipple line; it was smooth and not tender. Jaundice was not present. In other respects the physical examination gave negative results.

Immediately after admission to the ward, the patient had a generalized clonic convulsion lasting two or three minutes, during which time he became cyanotic. There was no carpopedal spasm, and the Chvostek and Trousseau signs were absent.

Calcium gluconate (10 cc. of a 10 per cent solution) was given intravenously, and a continuous infusion of 5 per cent dextrose in Ringer's solution was started. A dose of copper sulfate caused the child to vomit promptly (the vomitus did not have a garlic odor and was not luminous in the dark). A high colonic irrigation followed. Four doses of liquid petrolatum (4 cc. every six hours) were given by mouth.

A blood count taken immediately after the intravenous drip was started showed 4,200,000 red blood cells with 68 per cent hemoglobin and 7,600 white blood cells

From the Pediatric Service of Mount Sinai Hospital.

with 86 per cent polymorphonuclears. Blood taken from the jugular vein was found on examination to contain 11 mg. of calcium per hundred cubic centimeters and 180 mg. of cholesterol, 40 mg. of which was ester. The icteric index was 8. The first specimen of urine, obtained four or five hours after admission, contained a trace of albumin and from one to two granular and cellular casts per high power field, in addition to rare red blood cells; 1.7 per cent sugar, probably resulting from the dextrose infusion, was also present.

Course.—On the second day the temperature ranged between 100.2 and 104. The infant seemed more alert. The liver remained unchanged in size, and the spleen was palpable 2 cm. below the costal margin on the left nipple line. Pallor was extreme.

On the third day the scleras seemed slightly icteric. Small amounts of water given by mouth were retained, and that evening feedings of barley gruel were

Summary of Analyses of the Blood in a Case of Acute Phosphorus Poisoning

Date	Cholesterol Content, Mg. per 100 Cc.	Cholesterol Ester Content, Mg. per 100 Cc.	Sugar Content, Mg. per 100 Cc.	Urea Content, Mg. per 100 Cc.	Calcium Content, Mg. per 100 Cc.	Phosphorus Content, Mg. per 100 Cc.	Total Protein Content, Mg. per 100 Cc.	Albumin Content, Mg. per 100 Cc.	Globulin Content, Mg. per 100 Cc.	Takata-Ara Reaction	Icteric Index	Van den Bergh Reaction
10/ 1/35	180	40	...	..	11.0	...	...	...	...	..	8	.....
10/ 4/35	85	Trace	80	10	....	2.2	...	...	...	..	40	Dir. pr. + 3.0 mg.
10/ 5/35	...	..	85-102	..	....	...	...	...	...	..	..	.....
10/ 6/35	210	80	113	..	....	...	...	...	...	..	..	.....
10/ 7/35	...	..	106	..	....	...	...	...	...	+	..	.....
10/12/35	180	70	...	14	10.5	4.2	...	...	...	..	5	Dir. — 0.2 mg.
10/18/35	...	..	...	..	....	...	7.4	4.0	3.4	..	..	.....
10/24/35	155	40	...	..	....	...	...	...	...	+	6	Dir. — 0.2 mg.
10/31/35	...	..	...	..	....	...	...	...	...	+	..	.....
11/ 8/35	170	70	...	..	....	...	...	...	...	+	..	.....
11/11/35	175	85	...	..	....	...	...	...	...	..	..	.....
1/ 2/36	225	65	...	..	....	...	6.7	4.3	2.4	—	4	..... Dir. —
3/24/36	225	30	80	8	....	5.1	8.0	5.8	2.2	—	2	.....

started. The fluid requirements and part of the caloric requirements were satisfied by the continuous infusion. By the fourth day the icterus had become more intense; the icteric index was now 40. The content of cholesterol in the blood was 85 mg. per hundred cubic centimeters, and only a trace of cholesterol ester was present. The content of sugar in the blood at this time was 80 mg. per hundred cubic centimeters, a comparatively low figure in the face of the continuous dextrose infusion.

On the succeeding days the child's general condition improved rapidly. His diet was slowly increased, a ratio of 90 per cent carbohydrate to 10 per cent protein being maintained, not considering the small amounts of fat which were unavoidably present. The continuous intravenous drip was discontinued on the fifth day. After this change three determinations of the content of sugar in the blood were made during the day because of the fear of a possible hypoglycemia caused by hepatic insufficiency. The values varied from 85 to 102 mg. per hundred cubic centimeters. On the sixth day the blood sugar content was 113 mg. per hundred cubic centimeters and on the seventh day, 106 mg.

The temperature dropped slowly, reaching normal on the sixth day. At that time the edge of the liver was palpable 5 cm. below the costal margin and the icterus was less intense. The total cholesterol content had risen to 210 mg., and the amount of cholesterol ester, to 80 mg. The reaction to the Takata-Ara test for impaired liver function was positive.

The infant's general condition showed slow, steady improvement and he seemed to be doing well; however, on the eleventh day he vomited twice and had six loose stools. The following morning his temperature was 101 F. and he appeared somewhat dehydrated. The diet was considerably decreased, and saline solution

Fig. 1.—Roentgenogram of the long bones, showing a phosphorus band proximal to the epiphysial lines, six months after poisoning.

was given subcutaneously. He had five loose stools that day. On the thirteenth day he had a total of eleven loose stools, his temperature remained elevated and he appeared more drowsy than usual. Feedings by mouth were stopped, and a continuous intravenous drip of 5 per cent dextrose in Ringer's solution was once again started, followed the next day by a transfusion of 50 cc. of citrated blood. The diarrhea subsided promptly, and the child's general condition showed rapid improvement. The infusion was discontinued after three days, and the diet was cautiously increased. The patient's subsequent course in the hospital was uneventful, and a slow, steady gain in weight was noted.

Frequent analyses of the blood were made while the patient was being observed. These are summarized in the accompanying chart. The Wassermann, the Schick and the tuberculin tests gave negative results. The patient was discharged from the hospital in good health seven weeks after the accident. At that time the liver was palpable 3 to 4 cm. below the costal margin and the edge of the spleen, 1 to 2 cm. below the costal margin. Roentgenograms of the long bones did not show metallic lines.

The child was seen in the follow-up clinic on Jan. 2, 1936 (three months after the poisoning), at which time it was reported that he had been in excellent health.

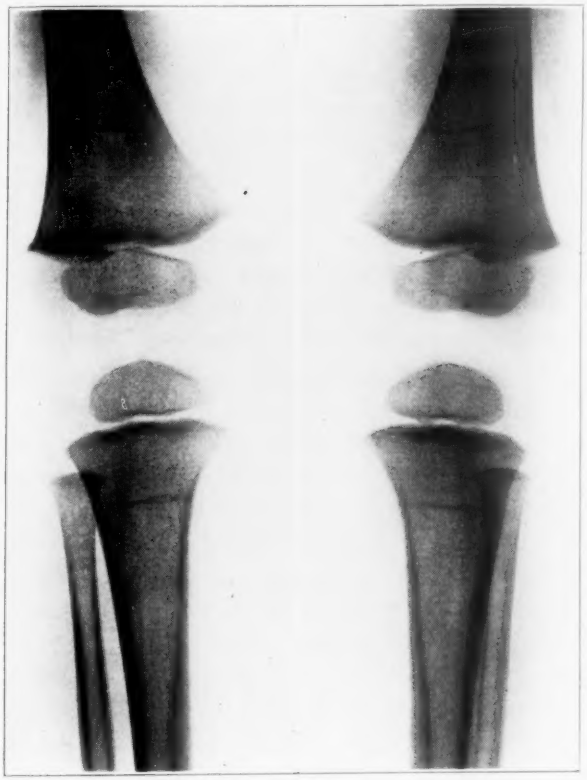

Fig. 2.—Roentgenogram taken fourteen months after poisoning, showing the phosphorus band still visible.

The liver and spleen were unchanged in size. A Takata-Ara test gave negative results, whereas four previous tests had elicited a positive reaction.

The patient was next seen three months later, when he was hospitalized for observation for one week. Since the preceding examination the child had enjoyed excellent health. At this time the edge of the spleen was just palpable. The edge of the liver was firm and smooth and extended 4 cm. below the costal margin in the right nipple line. The left border of the liver was palpable to the left of the midline of the abdomen. The distance between the upper and the lower borders of hepatic dulness measured 6.5 cm. Blood again taken for chemical analysis was found to have values within normal limits except for a low amount

of cholesterol ester. The test for dextrose tolerance showed a sugar content of 80 mg. during fasting, a rise to 100 mg. in one-half hour and a rise to 130 mg. in one hour. After two and three hours the content remained at 100 mg. There was no glycosuria. Roentgenograms of the long bones showed unusually dense lines of growth in all the extremities proximal to the epiphysial lines (fig. 1). It was felt that these represented phosphorus bands (*Phosphorschicht*). Since his initial hospitalization the child's weight had increased from 17 pounds 4 ounces (7,850 Gm.) to 21 pounds 3 ounces (9,650 Gm.).

When last seen in the follow-up clinic the boy was again in excellent health. Check-up of roentgenograms showed similar but less pronounced changes in the region of the epiphyses of all the long bones.

COMMENT

The literature contains numerous reports of fatalities in children from phosphorus poisoning following the ingestion of roach paste or the placing of fireworks in the mouth.[1] However, we were able to find only 2 previous reports containing studies of blood chemistry after acute phosphorus poisoning in man.[2]

It is not surprising that our patient was not brought to the hospital immediately after the ingestion of the phosphorus, since it is typical of patients with phosphorus poisoning to be comfortable for the first twenty-four to forty-eight hours. Yellow phosphorus has practically no local irritating effect on the stomach. It is rapidly absorbed and symptoms of poisoning usually do not become apparent until damage to the liver has progressed to the point of hepatic insufficiency. Usually this insufficiency occurs after a period varying from six or twelve hours to about two days, when vomiting and diarrhea start. The liver is tender to palpation and enlarges very rapidly. Jaundice becomes apparent and is soon followed by evidence of severe hypoglycemia, frequently terminating in convulsions and death.

On admission to the hospital, our patient was immediately given a continuous intravenous drip of 5 per cent dextrose in Ringer's solution. There is experimental, clinical and theoretic evidence for the statement that dextrose given intravenously should be the fundamental factor in

1. Stacy, W. C.: Dangers of Phosphorus in Fireworks, J. A. M. A. **77**:1514 (Nov. 5) 1921. Corwin, A. S.: New York State J. Med. **22**:475, 1922. Dwyer, H. L., and Helwig, F. C.: Phosphorus Poisoning in a Child from Ingestion of Fireworks, J. A. M. A. **84**:1254 (April 25) 1925. Swinton, C. F.: Brit. M. J. **2**:1080, 1927. Humphreys, E. M., and Halpert, B.: Acute Phosphorus Poisoning, Am. J. Dis. Child. **41**:354 (Feb.) 1931. Wentker, B. P., and Neuheiser, B. L.: J. Missouri M. A. **28**:220, 1931.

2. (*a*) McIntosh, R.: Acute Phosphorus Poisoning: Report of Case with Recovery, Am. J. Dis. Child. **34**:595 (Oct.) 1927. (*b*) McLean, S.: MacDonald, A., and Sullivan, R.: Acute Phosphorus Poisoning from Ingestion of Roach Paste, J. A. M. A. **93**:1789 (Dec. 7) 1929.

the treatment of acute phosphorus poisoning. Mann and Magath [3] demonstrated in dogs the importance of the liver in maintaining a constant level of blood sugar. It is believed that in phosphorus poisoning irritation precedes actual injury or necrosis of the hepatic cells; that small doses of phosphorus act as an irritant to the glycogenolytic mechanism of the liver, but that larger doses result in a deficiency of the chief function of the liver—that of maintaining the optimum blood sugar level.[4] McIntosh [2a] reported a case of acute phosphorus poisoning in a 16 month old boy in whose blood the sugar content was 35 mg. per hundred cubic centimeters, even though a clysis of dextrose had been given two hours before. McLean, MacDonald and Sullivan,[2b] reporting a case in an 18 month old boy who died nine hours after admission to the hospital, gave the blood sugar content as 55 mg. In our case a determination of the blood sugar content was not made until after four days of treatment with intravenous administration of dextrose; yet to our surprise we found a blood sugar level of only 80 mg. Evidence obtained in experimental studies of phosphorus poisoning indicates a very low blood sugar content, which was probably present in our patient on admission. We decided that this hypoglycemia was the most likely cause of the convulsion, a supposition all the more reasonable in view of the fact that the convulsion did not recur after dextrose was administered.

McIntosh treated his patient with a blood transfusion, with 70 cc. of 3 per cent dextrose intravenously and with 3 to 6 per cent dextrose by clysis every four or six hours. He noted sudden improvement in the patient's condition after the administration of the dextrose. McLean treated his patient with blood transfusion, with 120 cc. of 20 per cent dextrose intravenously and with 3 per cent dextrose subcutaneously. We likewise considered the use of blood transfusion during the acute stage in our patient, but we felt that a transfusion might overtax an already damaged liver. The advantage of the continuous intravenous drip of dextrose over the subcutaneous or interrupted intravenous administration seems obvious. With the liver unable to store sufficient amounts of glycogen, it becomes important to supply dextrose slowly and constantly to the blood stream until the liver can again take over its normal function.

Chemical analysis of the blood showed evidence of hepatic insufficiency. On first examination, when the icteric index was 8 (high

3. Mann, F. C., and Magath, T. B.: Studies on Physiology of the Liver: Effect of Removal of Liver on Blood Sugar, Arch. Int. Med. **30**:73 (July) 1922.

4. Althausen, T. L., and Thoenes, E.: Influence on Carbohydrate Metabolism of Experimentally Induced Hepatic Changes, Arch. Int. Med. **50**:58 (July) 1932.

normal), the total cholesterol content was 180 mg. and the amount of cholesterol ester 40 mg. On the fourth day jaundice appeared. The icteric index had risen to 40, and the van den Bergh test showed a positive prompt direct reaction. At this time the total cholesterol content had dropped to 85 mg. and only a trace of ester was present. Subsequently, as the child improved, the values for total cholesterol and cholesterol ester rose to between 155 and 225 mg. for the total cholesterol and between 30 and 85 mg. for the ester. The icteric index dropped to normal, with a negative direct van den Bergh reaction. It is of interest to note that, whereas the icteric index was normal and the van den Bergh reaction negative on the twelfth day, the Takata-Ara reaction remained positive for three months. During this entire period palpation of the liver showed enlargement.

The finding of an inorganic phosphorus value of 2.2 mg. at first seemed paradoxic. However, our finding of a low value for phosphorus agrees with the data in the previously published cases. McIntosh's patient had 3.4 mg. in the blood and McLean's 2.7. Neither in their cases nor in ours was there any clinical evidence of rickets. McLean felt that an inability to metabolize carbohydrates properly might account for the low phosphorus figures. Hess and Weinstock,[5] working with rats, observed the effect of phosphorus on the prevention of rickets. They fed the animals a rickets-producing diet supplemented by small doses (0.2 mg.) of elementary phosphorus. The results they obtained caused them to observe: "In view of the fact that this diet contains an excess of inorganic phosphorus, we were surprised to find that the addition of elementary phosphorus led to a diminution of the inorganic phosphorus in the blood—3.58 mg. in those animals receiving phosphorus, compared to 5.10 mg. in those receiving nothing but the low calcium ration." These authors agreed with Wegner,[6] who was afraid that phosphorus might actually induce rather than prevent rickets. Wegner felt that elementary phosphorus acts as an "osteoplastic irritant," thus stimulating calcification at the epiphyses to form the phosphorus band (*Phosphorschicht*), a transverse layer in the subepiphysial region consisting of abnormally dense bone. Roentgenograms of the long bones of our patient showed the presence of the typical *Phosphorschicht*. It seems probable that the ingestion of phosphorus stimulates calcification in the subepiphysial region at the expense of the rest of the bony structure. From this source a picture simulating rickets evolves, with a resultant low inorganic phosphorus value in the blood.

5. Hess, A. F., and Weinstock, M.: Value of Elementary Phosphorus in Rickets, Am. J. Dis. Child. **32**:483 (Oct.) 1931.

6. Wegner, cited by Hess and Weinstock.[5]

It should be emphasized at this time that roentgenograms taken two to four weeks after the ingestion of the poison failed to show metallic lines. The typical phosphorus band was first noted in the roentgenogram taken six months after the poisoning.

It is of some interest to note that the child did exceedingly well under treatment until the latter part of the second week. At that time, in spite of a very limited diet containing negligible amounts of fat, he began to have frequent loose stools and vomited on several occasions. Dietary modifications in an attempt to control this condition were of no avail, and typical alimentary intoxication developed. This new complication necessitated the use of continous dextrose infusion once more and prohibited all feeding by mouth. Under the treatment outlined by Karelitz,[7] the patient made an uneventful recovery from the episode. (McIntosh's patient began to have diarrhea on the seventh day, but this was easily controlled.) Frequent attempts to locate a focus of infection were made without avail. No other patients with alimentary intoxication were in the ward at that time. We feel that the complication was in the same class as alimentary intoxication due to a dietary indiscretion. In fact, for this particular patient, with extensive impairment of liver function, the diet of 1,200 cc. of skimmed milk, 35 Gm. of sugar and 40 Gm. of barley flour (667 calories, or 83 calories per kilogram) was probably excessive. Extreme caution should be exercised with such a patient when feedings are instituted. It is not surprising that this complication arose, since the theory that hepatic dysfunction is a cause of alimentary intoxication is still maintained by many authorities. All quantitative additions to the diet should be small, and it seems preferable to err on the side of temporary insufficiency rather than to run the risk of even slight excess, which can prove exceedingly harmful.

SUMMARY

A case of acute phosphorus poisoning (due to ingestion of roach paste) with recovery in an infant is reported. The method of treatment followed is outlined, particular emphasis being placed on the value of continuous infusion of dextrose solution. The results of studies of the blood chemistry in this case are compared with those in previously reported cases. The first appearance of the *Phosphorschicht* more than a month after the poisoning is demonstrated.

1097 Park Avenue.

2 West Seventy-Fifth Street.

7. Karelitz, S., and Schick, B.: Treatment of Toxicosis with Aid of Continuous Intravenous Drip of Dextrose Solution, Am. J. Dis. Child. **42**:781 (Oct.) 1931.

Progress in Pediatrics

EPIDEMIC DIARRHEA OF THE NEWBORN

IV. CLINICAL CONSIDERATIONS

HAROLD ABRAMSON, M.D.
AND
SAMUEL FRANT, M.D.
NEW YORK

There is probably no group of diseases of infancy and childhood presenting greater difficulties in etiology and diagnosis than that generally referred to as the diarrheal disorders. The voluminous and contradictory literature on the problem serves to emphasize the highly unsatisfactory state of knowledge of the causation and differentiation of the various primary and secondary enteric disturbances. In addition, the multiplicity of potential pathogens inhabiting the gastrointestinal tract and the uncertainty of their isolation by present bacteriologic methods combine to make a most confusing situation. Even more complicated is the problem of the diarrheal disorders which occur during the newborn period of life.

Since 1934 we have had under investigation a series of outbreaks of highly fatal diarrhea arising among newborn babies in the nurseries of lying-in hospitals. Our early experiences with the disorder were summarized in a preliminary discussion [1] which gave the essential features of the various outbreaks. The opinion was expressed that we were concerned with *a previously unrecognized clinical entity* affecting newborn infants during their customary period in obstetric nurseries. These conclusions were based on the remarkable similarity in clinical manifestations and in mode of spread of the disorder in the various outbreaks, specificity of the age groups involved, poor response to recognized therapeutic measures, constantly high morbidity and mortality rates, characteristic lack of pathologic lesions in spite of the clinical severity of the disorder, and uniform failure of bacteriologic, serologic and virus studies to reveal the causative agent.

From the Bureau of Preventable Diseases, New York City Department of Health, Dr. John L. Rice, Commissioner.

1. Rice, J. L.; Best, W. H.; Frant, S., and Abramson, H.: Epidemic Diarrhea of the New-Born: I. Preliminary Considerations on Outbreaks of Highly Fatal Diarrhea of Undetermined Etiology Among New-Born Babies in Hospital Nurseries, J. A. M. A. **109**:475-480 (Aug. 14) 1937.

In a subsequent publication [2] we detailed the measures that have been adopted by the New York City Department of Health to control these outbreaks of diarrhea among the newly born. Suggestions were advanced for prevention not only of this disorder but of infectious diseases in general among newborn infants in hospital nurseries. The proposed procedures were founded on the principles of surgical asepsis as applied to the nursing and medical care of the newborn, stress being laid on individual management.[2a] In addition, we [3] recently emphasized that greater attention must be directed toward lowering the persistently high mortality rates among babies during the newborn period of life. As is evidenced in the statistics on infant mortality of New York City,[4] exceedingly little has been accomplished in lowering mortality in the neonatal period. In fact, rate of death from diarrhea among the newborn has been steadily ascending for the past ten years. In great measure this increase may be attributed to the prevalence of the syndrome, epidemic diarrhea of the newborn.

It would seem opportune, therefore, to consider in detail the clinical manifestations of the disorder and its points of differentiation from other diarrheal diseases of infancy. It would also seem worth while to review briefly the few epidemics of similar nature that have been previously reported in the literature and to note in each the essential features which on analysis appear comparable to those described by us.

REVIEW OF THE LITERATURE

In the early literature little is found pertinent to our discussion. Reference is made occasionally to the occurrence of septic diarrhea among newborn infants.[5] Further, in considering the diarrheal dis-

2. Frant, S., and Abramson, H.: Epidemic Diarrhea of the New-Born: II. Control and Prevention of Outbreaks in Hospital Nurseries, J. Pediat. **11**:772-781 (Dec.) 1937.

2a. In modified form, these suggestions were adopted on Dec. 14, 1937, by the health department of New York in a sanitary code amendment regulating and governing lying-in institutions and nurseries for the newborn. The details have been published by Best, W. H.: Epidemic Diarrhea of the Newborn, J. A. M. A. **110**:1155 (April 9) 1938.

3. Frant, S., and Abramson, H.: Epidemic Diarrhea of the New-Born: III. Epidemiology of Outbreaks of Highly Fatal Diarrhea Among New-Born Babies in Hospital Nurseries, Am. J. Pub. Health **28**:36-43 (Jan.) 1938.

4. Bolduan, C., and Weiner, L.: Infant Mortality in New York City One Hundred Years Ago, J. Pediat. **7**:55-59 (July) 1935. Bolduan, C.: Course of Infant Mortality in New York City, Prev. Med. **6**:14-10 (July) 1936. Rice, J. L.; Barnard, M. W.; Duffield, T. J., and Blumenthal, J. L.: Infant Mortality in New York City, Am. J. Pub. Health **27**:701-706 (July) 1937.

5. Von Reuss, A.: The Diseases of the Newborn, London, John Bale, Sons & Danielsson, Ltd., 1920; Pathology of the Newborn Period, in von Pfaundler, M., and Schlossmann, A.: Diseases of Children, translated by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935, vol. 1, p. 456.

orders of infancy, a distinction must be made between the enteritis which occurred prior to the introduction of pasteurization of milk and that encountered at the present time. Modern practices of rendering milk safe for use and control of its distribution as well as general regulation of food and water supplies have considerably altered the clinical picture of enteritis. The spread of diarrheal diseases has also been influenced by recent advances in understanding of the problems of nutrition and of infant feeding and by widespread campaigns to educate mothers in the proper care of babies.

In 1928, the Dicks and Williams [6] reported an epidemic of enteritis associated with mastoiditis which occurred during the previous year among the infants at the Cradle, Evanston, Ill. Although the conditions under which this epidemic took place were not quite comparable to those described by us, the large number of fatal cases among babies in the neonatal period warrants a discussion of this outbreak. Eighty-eight babies were attacked and 27 died; of the latter, 23 were babies from 9 to 30 days of age. The morbidity rate, therefore, was 39.5 per cent and the case fatality rate 30.7 per cent. The disorder was characterized by sudden onset, diarrhea with grayish yellow, watery stools showing no blood and little mucus, loss in weight, late irregular temperature reactions and terminal bronchopneumonia. Complications involving the middle ear and the mastoid were commonly encountered. In 5 cases in which the outcome was fatal Morgan's bacillus was recovered on stool culture. Postmortem examinations showed acute hemorrhagic enteritis and swollen Peyer's patches. The investigators were of the opinion that the infection was of primary intestinal origin, Morgan's bacillus being the inciting agent, and that the otitis media and mastoiditis were secondary complicating factors.

In 1932, Jampolis and his collaborators [7] reported an epidemic of infectious diarrhea which occurred from February to June 1930 among newborn babies in a nursery of the Michael Reese Hospital of Chicago. They described a series of 34 newborn babies who, although lacking clinical signs of parenteral infection, had marked dehydration and severe diarrhea. The stools of these infants too were characterized by absence of blood or pus. Fourteen babies succumbed during the course of the outbreak. The outstanding condition revealed at necropsy consisted of acute enteritis involving the mucous membranes of the ileal portions of the intestines with relative absence of involvement of the colon. Extensive bacteriologic studies were made, and Bacillus mucosus

6. Dick, G. F.; Dick, G. H., and Williams, J. L.: The Etiology of an Epidemic of Enteritis Associated Mastoiditis in Infants, Am. J. Dis. Child. **35**: 955-963 (June) 1928.

7. Jampolis, M.; Howell, M. K.; Calvin, J., and Leventhal, M. L.: Bacillus Mucosus Infection of the New-Born, Am. J. Dis. Child. **43**:70-88 (Jan.) 1932.

capsulatus of the Friedländer type and anhemolytic streptococci were isolated from the nasal secretions, contents of the stomach and intestinal mucosa of a large number of babies, as well as from the throats and stools of 3 nursery maids. Removal of these nursery maids from ward duty was followed by a subsidence of the outbreak.

About three years then elapsed before further reports on the subject appeared. In 1935, Johnson and Kaake [8] reported their experiences with an outbreak of infectious diarrhea of the newborn which had occurred in the nursery of a small maternity hospital in Toronto during May and June 1933. Fifteen newborn infants ranging in age from 8 to 17 days became ill, and 9 died. The stools were watery and light yellow and contained no blood or pus. The role of etiologic agent was ascribed to Bacillus dispar, which was cultured from the noses and throats of 4 babies and from the stools of 11 babies and 1 nurse. The serum of 5 babies gave negative reactions for agglutinins when tested with homologous strains as antigens.

Shortly after the report just cited, Dulaney and Michelson [9] described an outbreak of diarrhea in the newborn during the winter of 1933-1934 at the Memphis General Hospital, Memphis, Tenn. The epidemic, lasting six months, involved babies between the fifth and the ninth day of life and had a mortality of 47 per cent. It is interesting to note that again the diarrheal stools were watery yellow or yellowish green and surprisingly free from blood, pus or mucus and that the clinical course of the disorder was marked by rapid loss of weight. Cultural studies revealed the presence of Bacillus coli mutabile in the stools of 18 of 27 sick babies. Blood agglutination tests again gave indefinite results.

The opportunity was then afforded us to follow [10] an epidemic in a nursery of a lying-in institution of Teaneck, N. J., during December 1934. Eleven of 20 sick infants died of the disorder, the clinical manifestations of which were similar to those of the outbreaks to be described subsequently. Extensive bacteriologic and pathologic studies gave no significant results.

The next published account was that of Durand,[11] who recorded an outbreak in a nursery of the Providence Hospital of Seattle, Wash.,

8. Johnson, M. M., and Kaake, M. J.: Bacteriologic Study of Three Small Epidemics of Infectious Diarrhea in Children, J. Pediat. **7**:65-69 (July) 1935.

9. Dulaney, A. D., and Michelson, I. D.: A Study of B. Coli Mutabile from an Outbreak of Diarrhea in the New-Born, Am. J. Pub. Health **25**:1241-1251 (Nov.) 1935. Oppenheimer, E.: Infant Mortality in Memphis, Bureau Publication 233, United States Department of Labor, Children's Bureau, 1936.

10. Unpublished data.

11. Durand, J. I.: Epidemic Diarrhea in a Hospital Nursery Apparently Caused by a Monilium, J. Pediat. **7**:726 (Nov.) 1935.

from January to June 1935. Twenty-three babies were affected, 14 of whom died in from two to ten days. The clinical picture was characterized by marked dehydration, low grade temperatures and acid, watery, yellow stools containing no blood. Necropsy gave essentially negative results. The epidemic was attributed to a monilia which was found in the stools of 5 babies and in the dextrose in solutions used for supplementary feeding.

Aïtoff and Daunay [12] then described the results of cultural studies of the stools of 5 newborn babies from 5 to 7 days of age, in whom there developed severe diarrhea while they were being cared for in the nursery of l'hôpital Lariboisière, Garches, France. The investigators recovered a gram-negative bacillus which showed cultural characteristics of an organism intermediary between the Shiga and the Flexner type of Bacillus dysenteriae. This organism was pathogenic to the mouse, rabbit and guinea pig.

Of added interest is the report by Yang and Wong [13] on an outbreak of alimentary intoxication among newborn infants in a nursery of the First Red Cross Hospital of Shanghai during the first two weeks of September 1935. Ten babies, ranging in age from 1 to 7 days, became ill, and 6 died. The duration of illness in those who died varied from three to ten days. The clinical picture was marked by watery stools with some mucus, vomiting, jaundice and the presence of granular casts in the urine. However, the sudden onset with fever, the presence of blood in the stools of 3 babies and the postmortem observation of diphtheritic ileocolitis and mesenteric lymphadenitis in 1 case and acute hemorrhagic catarrhal enteritis in another, cast doubt that the condition in these cases was similar to epidemic diarrhea of the newborn. Bacteriologic studies of the stools, blood, intestines and intestinal washings, as well as of the tap water, gave negative results. One specimen of milk examined at the time of onset of the outbreak showed many contaminating colon bacilli.

Two outbreaks which occurred in New York were next reported. In 1936 Barenberg, Levy and Grand [14] reported their experiences during July 1935 with an epidemic of infectious diarrhea affecting 32 newborn infants, 14 of whom died. The stools were yellow or greenish, watery, and acid in reaction. Slight amounts of mucus and curds were

12. Aïtoff, M., and Daunay, R.: Bacille dysentériforme: Agent pathogène probable d'une entérite grave, à caractère épidémique dans un service de nouveaunés, Compt. rend. Soc. de biol. **121**:110-112 (Jan. 11) 1936.

13. Yang, A. D., and Wong, A.: Intestinal Intoxication in Infants, Chinese M. J. **50**:390-398 (April) 1936.

14. Barenberg, L. H.; Levy, W., and Grand, M. J. H.: An Epidemic of Infectious Diarrhea in the New-Born, J. A. M. A. **106**:1256-1260 (April 11) 1937.

present, but no blood. Complications involving the respiratory tract and middle ear were commonly encountered. Bacteriologic studies and postmortem examinations failed to shed light on the nature of the disorder. The authors expressed the opinion that the condition was a specific syndrome occurring during the neonatal period and suggested that a specific virus might be the causative agent.

At the same time, Murphy and Mallozzi [15] detailed their bacteriologic studies on an epidemic of diarrhea among newborn babies which occurred during the late fall and winter months of 1935. Eighteen infants were involved; no deaths occurred. Routine examinations of the stools revealed in 1 instance a yeastlike fungus resembling Monilia albicans, a finding of interest in connection with the report of Durand [11] and the studies of Chaudhuri [16] on the relation of fungi to acute diarrhea of infants.

The paper by Craig [17] then appeared, describing 41 cases of severe gastroenteritis among newborn babies at the Royal Maternity Hospital, Edinburgh, over a period of three and one-half years. Seventeen of the cases occurred in minor epidemic form during the months of August and September 1935. Eleven infants succumbed to the disorder. In all cases the clinical features were unmistakably similar; they consisted of mild dyspepsia which appeared within from forty-eight to seventy-two hours, listlessness, frequent watery brown or green stools, irregular low grade fever, with a temperature which rarely exceeded 101 F. and fell by lysis, occasional vomiting, progressive dehydration, loss of weight and toxicity. Autopsy revealed hyperemia of the alimentary mucosa, swelling of Peyer's patches and mesenteric lymph nodes; ulceration was rarely noted. Bacteriologic cultures of material from the throat and of the stools gave no significant results. Craig believed that the disorder did not affect infants who were solely breast fed and that the condition was primarily an alimentary infection, probably related to the introduction of cow's milk into the infant's feeding.

In addition, attention is directed to the paper by Dummer and his associates [18] on an epidemic of benign lymphocytic meningitis which occurred in 1935 in Cincinnati. Brief reference is made to the fact that at the same time ". . . a severe form of diarrhea developed in

15. Murphy, J. R., and Mallozzi, M. A.: Fungus Findings in Diarrhea Outbreak in New-Born, Arch. Pediat. **53**:276-277 (April) 1936.

16. Chaudhuri, K. C.: The Role of Fungi and Anaerobes in Acute Diarrhoea of Infants, Indian J. Pediat. **4**:11-16 (Jan.) 1937.

17. Craig, W. S.: Acute Alimentary Catarrh in the New-Born, Lancet **2**:68-71 (July 11) 1936.

18. Dummer, C. M.; Lyon, R. A., and Stevenson, F. E.: Benign Lymphocytic Meningitis (Aseptic Meningitis), J. A. M. A. **108**:633-636 (Feb. 20) 1937.

newly born infants in the nurseries of several hospitals and this disease was accompanied by a severe toxaemia and a high mortality rate.[18a]

It should be emphasized here that the prevalence of this epidemic form of diarrhea among newborn babies is even more widespread than the literature would indicate. We have received communications[19] from physicians in additional large cities of the United States, who described the syndrome and inquired about its prevention and control.

In all reports thus far appearing in the literature, it is evident that certain common features predominate. In brief, the authors describe an epidemic form of severe diarrheal disease which has no seasonal preference and which affects newborn babies in hospital nurseries. The occurrence of watery, yellow diarrheal stools with little or no mucus and no blood is outstanding, as well as the consequent signs of dehydration and loss of weight. Evidence of early manifest parenteral disease is notably lacking, fever reactions are late, and the complications originate essentially in the ear and in the respiratory tract. Pathologic lesions are characteristically meager and insignificant, and the varied results of the bacteriologic studies are inconclusive. It is true that the reaction of the newborn to a variety of infections may be manifested by the common clinical picture of dehydration and intoxication. Yet proof is lacking as to whether the organisms to which the various outbreaks have been ascribed were the primary causative agents or merely secondary invaders.

CLINICAL SYNDROME

If one is to clarify the clinical picture of the disease, it will not suffice merely to enumerate symptoms and signs. The symptomatic train of acidosis, coma, exsiccosis and death which results from marked loss of salt and water from the body is well known and need not be detailed here. Recognition and differentiation of the disorder lie rather in an appreciation of the conditions underlying the outbreak and in an understanding of the sequence of its related events.

Predisposing Factors.—At the outset it should be borne in mind that one is dealing primarily with a group of newborn babies, delivered at full term or prematurely, congenitally debilitated or congenitally diseased, all receiving customary group care in the usual crowded, open nursery. These babies are handled in their daily routine by an under-

18a. The details of an additional outbreak in the nurseries of a hospital in New York were recently described. The outbreak began in January 1937. Of 129 newborn babies who were exposed, 52 became ill and 15 died. Search for a specific cause of the epidemic yielded negative results (Greenberg, M., and Wronker, B. M.: An Outbreak of Epidemic Diarrhea in the Newborn, J. A. M. A. **110**:563 [Feb. 19] 1938).

19. Personal communications to authors from pediatricians in Cleveland, Rochester, Buffalo, Baltimore, Milwaukee and Newark.

staffed nursing personnel who are untrained in the detailed technic of aseptic nursing care. In addition, there is incessant transportation of the babies for feeding from the nursery to their mothers in the open maternity ward and back. This continual manipulation is further augmented by frequent medical examination of the babies and by the treatment ordered. There is likewise a common lack of proper equipment in nursery, formula room, laundry and utility room and of segregated facilities for the care of premature and immature babies, as well as a lack of facilities for immediate isolation of sick infants. Emphasis must also be placed on the characteristically marked susceptibility of these newly born babies to infection and on the exceptional rapidity of spread of disease from one baby to another during the neonatal period of life. All these conditions set the stage for outbreaks of severe and often fatal infections among the newborn in hospital nurseries. At times, preexisting disorders such as thrush and impetigo may also lower the resistance of the babies and prepare them for invasion by infective agents.

Typical Outbreak.—The clinical manifestations of epidemic diarrhea of the newborn are probably best described by presenting chronologically the events in a typical outbreak. Table 1 gives the details of such an outbreak, which occurred in a large general hospital giving maternity care to the poorer classes of the city. The maternity division of this hospital occupies one floor of the main building and has two nurseries of equal size connected by a common bathing and diapering room. The probable date of onset of the first 2 instances of the disorder was May 17; the patients were 2 white infants who had been normally delivered at full term, with weights at birth well beyond the average. These babies had loose stools on the fourth and fifth postnatal days. The next 6 cases occurred at irregular intervals up to June 7, after which crops of new cases appeared in daily succession. This initial erratic appearance of cases, with latent or interval-free periods during which the epidemic is simmering to complete activity, is characteristic of all outbreaks. Recognition of this early phase is of epidemiologic importance, since at this point preventive measures can be taken to combat most effectively the spread of the disorder and to avoid excessively high morbidity and mortality rates. As seen in table 1, hesitancy in suspending maternity services and in closing the nurseries to further admissions, or the use of makeshift arrangements, serve by increasing the number of contacts to pile up the cases and inevitably to cause a high incidence of death. In passing, it should be added that any instance of diarrhea among a group of newborn babies should prompt an immediate check on the condition of all babies in the nursery, as well as a review of all current case records, that it may be determined whether the epidemic form of the disease exists.

TABLE 1.—*Summary of a Typical Outbreak of Epidemic Diarrhea of the Newborn in a Nursery* *

Case Number	Sex	Color	Date of Birth	Term of Gestation	Weight at Birth	Onset of Loose Stools	Age at Onset, Days	Date Discharged as Normal	Weight on Discharge	Date of Transfer to Pediatric Service	Readmitted to Hospital to Pediatric Service	Date Discharged as Recovered	Age on Recovery, Days	Weight on Discharge	Date of Death	Age at Death, Days	Weight at Death	Duration of Illness, Days	Comment
1	♀	W	5/12/37	Fu	9-12	5/17/37	5	5/21/37 (A.O.R.)	9-11	.....	.....	.....	..	....	.....	..	....	?	Otitis media
2	♂	W	5/13/37	Fu	8- 4	5/17/37	4	5/22/37 (A.O.R.)	8- 6	.....	.....	.....	..	....	.....	..	....	?	
3	♀	W	5/ 9/37	Fu	6- 0	5/18/37	9	5/19/37	6-10	.....	.....	.....	..	....	.....	..	....	?	Pyoderma
4	♀	W	5/14/37	Fu	7- 8	5/20/37	6	5/22/37 (A.O.R.)	7- 7	.....	.....	.....	..	....	.....	..	....	?	Pyoderma
5	♀	C	5/16/37	Fu	7-10	5/20/37	4	.....	....	5/20/37	.....	5/24/37	8	7- 8	.....	..	...	4	
6	♀	W	5/18/37	Fu	6-12	5/23/37	5	5/26/37	6-12	.....	.....	.....	..	....	.....	..	....	?	
7	♀	C	5/ 8/37	Fu	6- 2	5/29/37	21	5/17/37	6- 9	.....	.....	.....	..	....	.....	..	....	?	
8	♂	W	5/25/37	Fu	5- 2	6/ 3/37	10	6/ 2/37	5- 4	.....	6/ 5/37	.....	..	....	6/15/37	22	4- 0	12	Thrush
9	♂	W	5/14/37	Pre	4-10	6/ 7/37	24	6/ 1/37	5- 0	.....	6/10/37	.....	..	....	6/11/37	28	4-10	4	Otitis media; thrush
10	♀	W	5/23/37	Fu	6- 7	6/ 7/37	15	6/ 5/37	6-13	.....	6/11/37	6/28/37	36	7-11	.....	..	....	21	
11	♂	C	5/31/37	Pre	4-12	6/ 7/37	7	.....	....	.....	.....	.....	..	....	6/ 9/37	9	3-15	2	Thrush
12	♂	W	6/ 4/37	Fu	7-12	6/ 8/37	4	.....	....	6/ 8/37	.....	.....	..	....	7/ 3/37	29	3- 0	23	Otitis media
13	♂	W	6/ 5/37	Fu	7- 4	6/ 8/37	3	.....	....	6/ 8/37	.....	7/ 7/37	32	6-15	.....	..	....	34	Otitis media
14	♂	C	6/ 1/37	Pre	4- 8	6/ 9/37	8	.....	....	.....	.....	.....	..	....	6/11/37	10	4- 1	2	Otitis media
15	♂	C	6/ 1/37	Pre	4- 7	6/ 9/37	8	.....	....	.....	.....	.....	..	....	6/11/37	10	4- 0	2	Gonococcic conjunctivitis
16	♂	W	6/ 3/37	Fu	7- 0	6/ 9/37	6	6/11/37	6-14	.....	.....	.....	..	....	.....	..	....	?	
17	♀	W	6/ 4/37	Fu	7- 8	6/ 9/37	5	6/12/37 (A.O.R.)	7-12	.....	.....	.....	..	....	.....	..	....	?	
18	♀	W	6/ 4/37	Fu	7- 8	6/ 9/37	5	6/11/37 (A.O.R.)	7- 4	.....	.....	.....	..	....	.....	..	....	?	
19	♀	C	6/ 7/37	Fu	7- 2	6/ 9/37	2	.....	....	.....	.....	6/15/37	8	7-14	.....	..	....	6	
20	♂	C	6/ 4/37	Pre	4- 9	6/10/37	6	.....	....	.....	.....	.....	..	....	6/13/37	9	4- 3	3	Thrush
21	♀	W	6/ 4/37	Fu	7- 8	6/10/37	3	.....	....	6/12/37	.....	6/26/37	22	7- 4	.....	..	....	16	Otitis media
22	♀	C	6/ 7/37	Fu	6- 9	6/10/37	3	.....	....	6/11/37	.....	6/20/37	13	6-10	.....	..	....	10	
23	♀	W	6/ 9/37	Fu	8- 2	6/10/37	1	.....	....	6/12/37	.....	6/18/37	9	8- 0	.....	..	...	8	
24	♀	C	6/ 9/37	Fu	6-14	6/10/37	1	.....	....	.....	.....	6/16/37	7	6- 5	.....	..	....	6	
25	♀	C	6/ 3/37	Fu	8-12	6/11/37	8	.....	....	6/11/37	.....	6/29/37	26	9- 0	.....	..	....	18	Otitis media
26	♂	C	6/ 7/37	Fu	7-14	6/11/37	4	.....	....	6/11/37	.....	.....	..	....	7/ 1/37	23	5- 0	20	
27	♂	C	6/ 5/37	Fu	7- 4	6/12/37	7	.....	....	6/12/37	.....	.....	..	....	6/23/37	18	5- 7	11	Terminal pneumonia
28	♀	C	6/ 8/37	Fu	8- 0	6/12/37	4	.....	....	6/12/37	.....	6/30/37	22	7- 3	.....	..	....	18	
29	♀	W	6/ 8/37	Pre	4-13	6/13/37	5	.....	....	6/17/37	.....	.....	..	....	6/22/37	14	4- 0	9	
30	♀	W	6/ 8/37	Pre	4-11	6/14/37	6	.....	....	6/14/37	.....	.....	..	....	6/15/37	7	3-14	1	
31	♂	C	6/ 8/37	Fu	6- 8	6/14/37	6	6/17/37 (A.O.R.)	6- 7	.....	.....	.....	..	....	.....	..	....	?	
32	♀	W	6/ 9/37	Fu	6- 3	6/17/37	8	6/17/37 (A.O.R.)	6- 4	.....	.....	.....	..	....	.....	..	....	?	
33	♂	C	6/ 3/37	Fu	8- 7	6/20/37	20	6/12/37	8- 2	.....	6/23/37 (see comment)	7/ 4/37	31	8-15	.....	..	....	14	Admitted to another hospital
34	♂	C	6/ 9/37	Fu	6- 8	6/20/37	11	6/16/37	6- 0	.....	6/21/37 (see comment)	.....	..	....	6/22/37 (see comment)	12	4-13	2	Admitted to and died in another hospital
35	♀	C	5/27/37	Fu	5-13	6/22/37	25	.....	....	.....	.....	6/28/37	32	6- 9	.....	..	....	6	Congenital abnormality of heart
36	♂	C	6/ 7/37	Fu	6- 3	6/23/37	16	6/15/37	6- 0	.....	6/30/37 (see comment)	7/12/37	35	6-11	.....	..	....	17	Admitted to another hospital; blood in stools ?

* The cases are arranged according to the date of onset of loose stools. The signs have the following meanings: ♂, male; ♀, female; W, white; C, Negro; Pre, premature; Fu, full term; A.O.R. at own risk; ?, data not available (babies could not be traced). The outbreak occurred in the ward service. The probable onset occurred on May 17, 1937; the last known case on June 20. The first known death occurred on June 9, and the last on July 8. Of the 36 cases, 2 were admitted from other hospitals, 2 died in the ward service, 2 died in another hospital, and 6 were admitted to the pediatric service.

Incubation Period.—Analysis of 190 cases shows that the period of incubation varies from two to twenty-one days, the most frequent period being four days and the median six and five-tenths days (fig. 1 *A*). However, the period may be as brief as one day, as determined by the

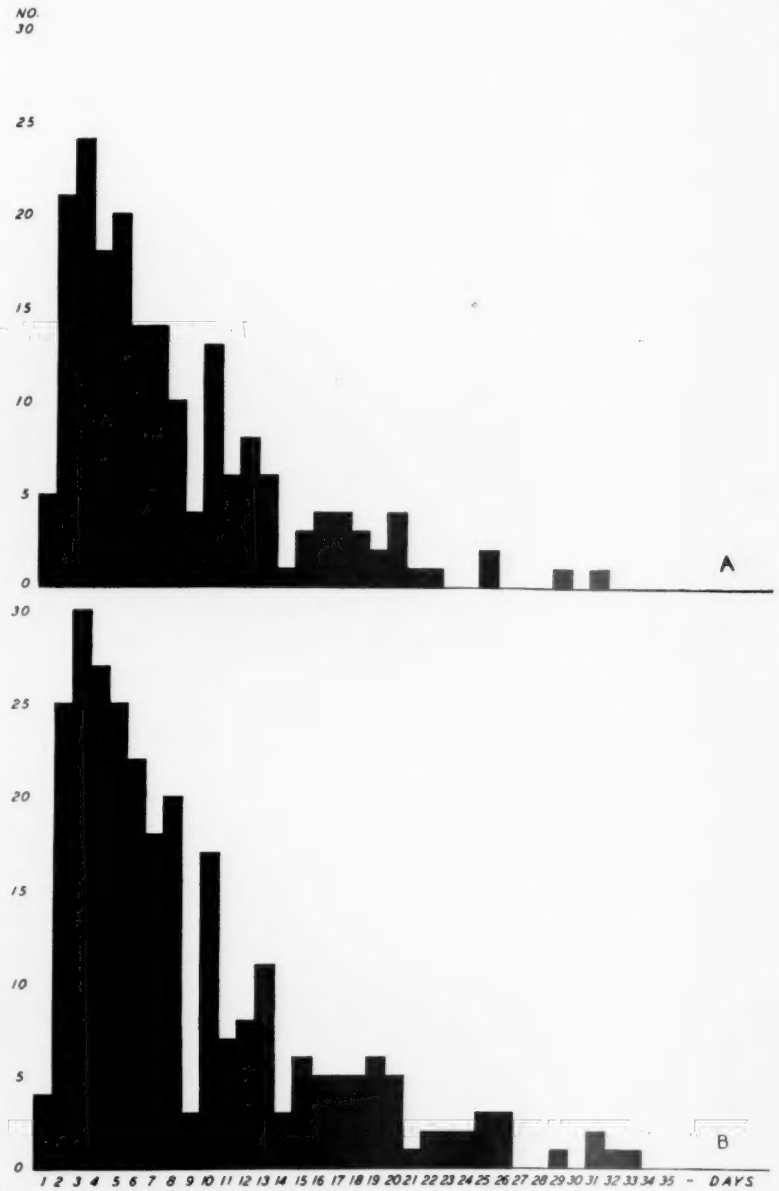

Fig. 1.—*A*, period of incubation in 190 cases of epidemic diarrhea of the newborn as determined by the initial occurrence of loose stools. *B*, age at the onset of illness in 270 cases as determined by the first appearance of loose stools.

initial occurrence of loose stools in infants placed in an infected nursery after the onset of an outbreak, or it may be as long as thirty-one days, as evidenced by the beginning of illness in babies discharged as normal and subsequently readmitted for treatment of the disorder.

Age at Onset.—The age at onset of illness, as determined also by the first occurrence of loose stools, is shown in figure 1 *B*, which represents an analysis of 270 cases. The sharp limitation of the disorder to the newborn period is evident. Most of the babies were attacked at ages of from 2 to 14 days. The median age is 7 days.

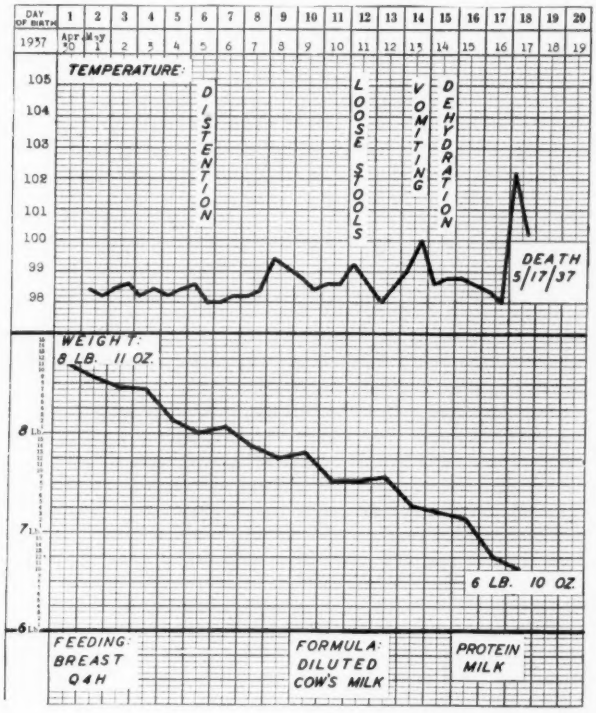

Fig. 2.—Clinical course of a case of epidemic diarrhea of the newborn in which death occurred. A normal Negro boy had an uncomplicated delivery and at birth weighed 8 pounds and 11 ounces (3,941 Gm.). Loose stools developed on the eleventh postnatal day, and the baby died on the eighteenth day of life, in extreme intoxication and weighing about 6 pounds and 10 ounces (3,005 Gm.).

SYMPTOMATOLOGY

Stage of Invasion.—The stage of invasion is brief and is characterized by prodromal signs of diminishing appetite, failure to gain weight or even slight loss in weight, listlessness, occasional vomiting, distention, normal temperature and increase in frequency of stools. The clinical course may progress no further in cases of mild involvement and in cases in which the disease is recognized and treated early. But as the

outbreak gains headway, the prodromal symptoms are less marked and the condition becomes more acute in onset, more rapid in course and increasingly severe. The complete clinical picture of intense intestinal intoxication is soon evident.

Toxic Stage.—In the toxic stage the stools continue to increase in frequency; soon they become loose, very watery and acid, and evacuation is explosive. Little or no mucus is present and no pus or blood. Early the color is characteristically yellow, but subsequently it may become greenish or brownish. Accompanying the marked loss of body fluids in the stools, the signs of dehydration and acidosis ensue. The baby becomes increasingly drowsy, to the point of coma. Other signs and symptoms referable to the central nervous system are lacking.

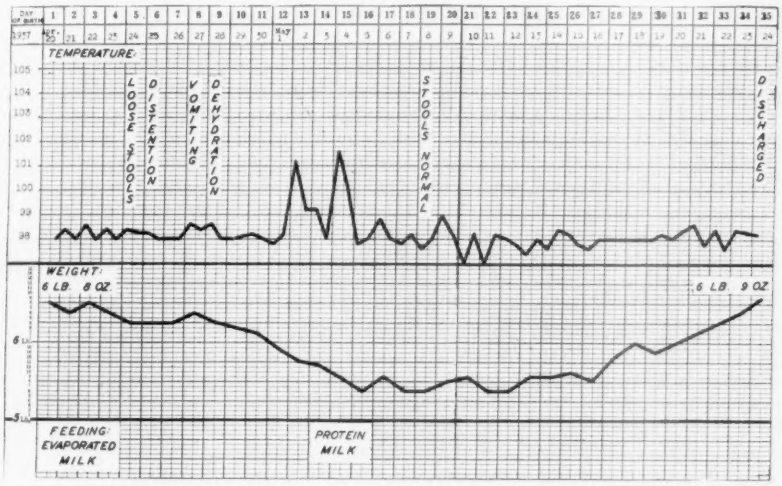

Fig. 3.—Clinical course of a case of epidemic diarrhea of the newborn in which recovery occurred. A previously healthy Negro boy had normal delivery and at birth weighed 6 pounds and 8 ounces (2,948 Gm.). He showed the first signs of loose stools on the fifth postnatal day. He was discharged cured on the thirty-fifth postnatal day, having regained his lost weight.

When the baby is aroused the cry is short and feeble. The skin is ashen gray, dry and inelastic; the eyeballs and fontanels are sunken, and the breathing is seen to be irregular. Loss of weight is marked, amounting at times to as much as a pound (454 Gm.) or more in a day. Abdominal distention is greater and is refractory to treatment. The body temperature varies between 99 and 101 F., seldom being higher. Aside from slight and questionable redness of the throat, physical examination when the condition is uncomplicated reveals little of significance in the nature of involvement of the respiratory tract or other parenteral disease. Laboratory examination of the blood shows high erythrocyte

counts and hemoglobin content. The leukocytes are relatively increased in number. The marked concentration of the blood is also reflected in high total protein and nonprotein nitrogen content. The carbon dioxide-combining power is exceedingly low, ranging frequently from 15 to 5 volumes per cent. The presence of albumin and casts in the urine gives some evidence of irritation of the kidney. When patients have these severe symptoms death rapidly ensues.

Complications.—In infants living long enough, a late rise in temperature may indicate the onset of complications, which are mainly otitis media and bronchopneumonia. Occasionally secondary invasion of the body by pyogenic organisms occurs, resulting in terminal sepsis and in suppurative foci of infection.

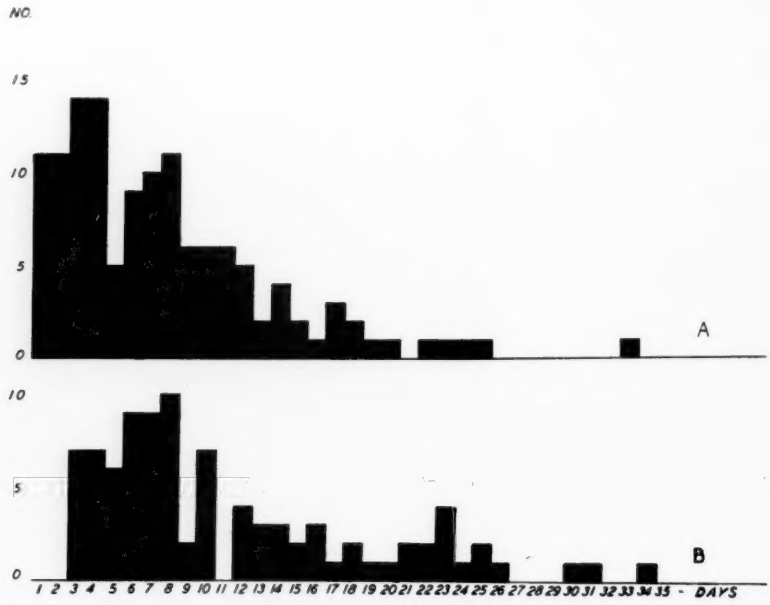

Fig. 4.—*A,* duration of illness in 129 cases of epidemic diarrhea of the newborn in which the patients died. *B,* duration of illness in 91 cases in which the patients recovered.

Stage of Recovery.—In cases of less severe involvement the stage of recovery is ushered in by cessation of loss in weight, improvement in tissue turgor and diminution in frequency of stools. The baby shows a desire for food, and its cry is stronger.

Duration of Illness.—Of course the duration of illness will be influenced by such factors as severity of infection, the time when the diagnosis is made and treatment begun, the presence of complications and the general condition of the baby at the onset of illness. Analysis of 129 cases in which death occurred shows that the duration of illness varied from one to twenty-five days, the median being seven days

TABLE 2.—*Summary of an Outbreak of Epidemic Diarrhea of the Newborn Involving Babies in Ward, Semiprivate and Private Nurseries**

TABLE 2.—*Summary of an Outbreak of Epidemic Diarrhea of the Newborn Involving Babies in Ward, Semiprivate and Private Nurseries* *

Case Number	Sex	Service	Nursery	Date of Birth	Term of Gestation	Weight at Birth	Onset of Loose Stools	Age at Onset, Days	Date Discharged as Normal	Weight on Discharge	Date of Transfer to Pediatric Service	Readmitted to Hospital in Pediatric Service	Discharged Recovered	Age on Recovery, Days	Weight on Discharge	Date of Death	Age at Death, Days	Weight at Death	Duration of Illness, Days	Comment
1	♂	W	M	11/20/36	Pre	5- 0	11/26/36	6	.....	....	.....	.....	.....	..	....	12/ 3/36	14	3-7	7	
2	♀	W	M	11/29/36	Fu	5-14	12/ 2/36	3	11/ 8/36	6-10	.....	.....	.....	..	....	12/26/36	27	?	24	Died at home
3	♀	W	M	11/24/36	Pre	4- 0	12/ 7/36	13	.....	....	12/7/36	.....	.....	..	....	12/13/36	19	3-0	6	Terminal pneumonia
4	♀	P	V	12/18/36	Fu	9- 3	12/26/36	8	12/27/36	8-13	.....	1/10/37	.....	..	....	1/11/37	23	?	16	
5	♀	W	M	12/21/36	Fu	9-13	12/26/36	5	1/ 1/37	8-15	.....	1/ 9/37	.....	..	....	1/12/37	22	8-0	17	Terminal pneumonia
6	♀	W	M	12/11/36	Fu	8- 7	12/27/36	16	12/19/36	8- 5	.....	12/27/36 (see comment)	.....	..	....	12/30/36	11	?	3	Admitted to and died at another hospital
7	♂	W	M	12/29/36	Fu	7-14	12/31/36	2	.....	....	12/31/36	.....	.....	..	....	1/ 8/37	9	?	8	
8	♂	P	V	12/ 9/36	Fu	6- 2	1/ 3/37	25	12/18/36	6- 2	.....	1/ 3/37	1/16/37	13	4- 5	1/22/37	44	?	19	Died at home
9	♂	W	M	12/ 6/36	Fu	8-12	1/ 4/37	29	1/ 4/37	7- 9	.....	1/14/37	.....	..	....	1/14/37	29	?	10	
10	♀	W	M	12/20/36	Fu	7-14	1/ 7/37	18	12/29/36	6-13	.....	1/ 7/37 (see comment)	.....	..	....	1/ 8/37	19	?	1	Admitted to and died at another hospital
11	♀	S.P.	M	12/23/36	Fu	7-12	1/10/37	18	.....	....	.....	.....	.....	..	....	1/13/37	19	6-3	3	
12	♀	W	M	1/10/37	Pre	5- 0	1/17/37	7	.....	....	.....	.....	.....	..	....	1/21/37	11	4-3	4	
13	♂	W	M	1/16/37	Fu	6-11	1/18/37	2	.....	....	.....	.....	.....	..	....	2/ 2/37	17	?	15	
14	♂	W	M	1/16/37	Fu	7-12	1/18/37	2	1/23/37	6-12	.....	.....	.....	..	....	2/12/37	27	?	25	Died at home
15	♂	P	V	1/11/37	Pre	5- 0	1/19/37	8	.....	....	.....	.....	.....	..	....	1/27/37	16	5-8	8	
16	♂	P	V	1/12/37	Pre	5- 4	1/19/37	7	.....	....	.....	.....	2/14/37	33	?	.....	..	...	26	
17	♀	W	M	1/16/37	Fu	8- 2	1/19/37	3	.....	....	1/26/37	.....	.....	..	....	1/31/37	15	?	12	Terminal pneumonia
18	♀	P	V	1/15/37	Fu	7- 3	1/21/37	6	.....	....	.....	.....	2/15/37	31	?	.....	..	...	25	
19	♀	P	V	1/ 7/37	Fu	8-10	1/23/37	16	.....	....	.....	.....	1/28/37	21	7-12	.....	..	...	5	
20	♂	S.P.	M	1/18/37	Fu	7-11	1/23/27	5	1/29/37	6- 6	.....	1/30/37	.....	..	....	1/30/37	12	?	7	
21	♀	W	M	1/21/37	Fu	7-12	1/25/37	4	.....	....	1/25/37	.....	.....	..	....	2/ 1/37	11	6-3	7	
22	♀	P	V	1/16/37	Fu	7- 9	1/26/37	10	1/25/37	7- 7	.....	1/26/37	.....	..	....	2/ 1/37	16	?	6	
23	♂	W	M	1/19/37	Fu	5-14	1/26/37	7	.....	....	1/29/37	.....	.....	..	....	2/ 3/37	13	?	7	
24	♀	W	M	1/25/37	Fu	7- 2	1/26/37	1	.....	....	2/ 3/37	.....	2/ 4/37 (A.O.R.)	10	7-10	.....	..	...	7	
25	♀	P	V	1/17/37	Fu	7- 7	1/27/37	10	1/25/37	7- 7	.....	.....	.....	..	....	2/ 3/37	17	?	7	Died at home
26	♂	S.P.	M	1/22/37	Fu	7- 6	1/30/37	8	1/30/37	7-10	.....	2/ 5/37	.....	..	....	2/ 1/37	10	6-6	2	
27	♀	W	M	1/25/37	Fu	6- 2	1/30/37	5	2/ 5/37	5- 8	.....	2/ 8/37	.....	..	....	2/ 8/37	14	?	9	
28	♂	S.P.	M	1/25/37	Fu	7- 2	1/31/37	6	.....	....	.....	.....	.....	..	....	2/ 3/37	9	?	3	Terminal pneumonia
29	♂	W	M	1/ 1/37	Fu	5- 8	2/ 1/37	31	1/10/37	5- 9	.....	2/ 7/37	.....	..	....	2/10/37	40	?	9	
30	♂	P	V	1/19/37	Fu	7- 0	2/ 1/37	13	1/28/37	7- 7	.....	2/ 6/37	.....	..	....	2/ 7/37	19	?	6	
31	♀	W	M	1/30/37	Fu	10-12	2/ 1/37	2	.....	....	2/ 1/37	.....	2/14/37 (A.O.R.)	15	?	.....	..	...	13	
32	♂	W	M	1/30/37	Pre	2-14	2/ 2/37	3	.....	....	.....	.....	.....	..	....	2/ 5/37	6	6	3	Terminal pneumonia
33	♂	S.P.	M	1/27/37	Fu	6- 7	2/ 3/37	7	2/ 5/37 (A.O.R.)	6-14	.....	2/ 3/37	.....	..	....	2/14/37	18	?	11	Terminal pneumonia
34	♂	W	M	1/30/37	Pre	3- 2	2/ 6/37	7	.....	....	.....	.....	.....	..	....	2/11/37	12	?	5	Terminal pneumonia

* The cases are arranged according to the date of onset of loose stools. The signs have the following meanings: ♂, male; ♀, female; W, ward; S.P., semiprivate; P, private; Pre, premature; Fu, full term; A.O.R., at own risk; ?, data not available (hospital records incomplete). The probable onset of the outbreak occurred on Nov. 26, 1937, the last known case, on February 6. The first known death occurred on December 3 and the last on February 14. Of 229, (121 ♂, 108 ♀) white babies exposed, 34 (17 ♂, 17 ♀) became ill (14.8 per cent). Of the babies attacked, 29 (16 ♂, 13 ♀) died (mortality rate, 12.7 per cent; case fatality rate, 85.3 per cent). The babies were predominantly breast fed, with supplements of cow's milk, evaporated milk and other artificial feedings.

(fig. 4 *A*). In 91 cases in which the patient recovered the median duration of illness was just under nine days and ranged from three to twenty-six days (fig. 4 *B*).

EPIDEMIOLOGY

An outbreak of epidemic diarrhea of the newborn in a nursery appears to spread from one baby to those in adjacent bassinets, regardless of the sex, race or color of the infants or of the type of feeding they have been receiving. Other nurseries in the same institution may be contaminated by unwitting transfer to these clean nurseries of an infant previously exposed or in the initial stage of the disease. In uncontrolled outbreaks, a wide scattering of sick infants occurs. Some exposed babies who are discharged in apparently good condition are soon readmitted to the pediatric service exhibiting manifest signs of the disease (table 1, cases 8, 9, 10; table 2, cases 4, 5, 8, 9, 20, 22, 26, 27, 29, 30, 33). Others are admitted to neighboring hospitals for treatment (table 1, cases 33, 34, 36; table 2, cases 6, 10) or are cared for and die at home (table 2, cases 2, 8, 14 and 25). This series of events serves to emphasize the necessity of recognizing the first signs of an outbreak so that the nursery may be closed immediately and all contacts may be observed carefully over a sufficient period for evidence of the disease. In this way, prompt treatment can be instituted early in the course of the illness and death rates can be lowered. In passing, it should be pointed out that the specificity of the disease for infants in the newborn period of life is brought out by the fact that to date there has been no evidence of cross infection among the older infants and children or adult personnel in the open pediatric wards to which the sick infants have been admitted; neither has the disorder occurred among the members of the families of ill infants who have been cared for at home.

Further light is shed on the possible mode of spread of an outbreak by table 2. The main features of the outbreak detailed in table 1 are here duplicated and need not be discussed again. Interest lies rather in the general physical arrangement of the maternity and newborn services of the hospital in which this outbreak occurred, in relation to the spread of the disease. Babies in the usual three classes of hospital service were involved, namely, ward, semiprivate and private. The obstetric department of this particular hospital occupies two floors of the main building. The ward and semiprivate maternity services and their nurseries are situated on one floor, as are the common labor and delivery rooms. The latter also serve the private maternity patients, who after delivery are cared for on an upper floor of the hospital. The private rooms are completely separated from the ward and from semiprivate facilities by an intervening floor of wards for patients requiring medical and surgical

care. A separate nursery is maintained on the private floor for babies who receive private obstetric care. In another wing of this upper floor are the pediatric wards and the formula kitchen, which serves all infants and children in the hospital. The nursing and medical staffs rotate from one type of service to another.

As indicated in the table, the outbreak began in the ward nursery on the lower floor. In 2 additional babies there diarrhea subsequently developed. Of interest is the fact after a latent period of about three weeks, 2 babies became ill on the same date, 1 a private patient (case 4), on the eighth postnatal day, and the other, a ward patient (case 5), on the fifth day of life. Since these infants were cared for in widely separated nurseries, the simultaneous onset of illness offers a highly suggestive clue in tracing out the path of spread of the disorder. Naturally, it is to common points of exposure that attention must be directed in the search for the origin of the infection. In the routine of delivery and postnatal care of the babies, several common sources of contact are suggested, as, for example, the labor and delivery rooms, the laundry and the formula kitchen. Also to be considered in this connection are nursing and medical staffs, dietitians and lay employees on rotating duty in any of the just cited divisions of the obstetric service, as well as in the nurseries and in the laundry.

BACTERIOLOGY

Along the avenues of approach just described the infective agent of the disorder has been sought. Despite repeated bacteriologic studies of the stools and nasopharyngeal secretions of the babies and of all adults in contact with them, no consistent results have been obtained to date. Nor has success attended serologic and virus studies. A careful review of the records of the mothers for evidence of disease of the respiratory tract or of gastrointestinal disease and repeated similar investigation of the maternity service and laundry personnel prior to and during the course of the outbreaks have failed likewise to reveal any significant clues.

At first glance, it might seem that a micro-organism of the dysentery group is the cause. On the basis of agglutination studies, Felsen and Osofsky [20] concluded that incidence of dysentery in the newborn is causally related to the infants' general lack of humoral antibodies to bacteria of the dysentery group. If this assumption is correct, it should be possible to demonstrate in many such sick infants rising dysentery agglutination titers during the course of illness or after recovery. Like-

20. Felsen, J., and Osofsky, A. G.: Susceptibility of the New-Born to Acute Bacillary Dysentery: Serologic Data on the Placental Transmission of Antibodies to Bacillus Dysenteriae, Am. J. Dis. Child. **53**:975-984 (April) 1937.

wise, repeated cultures of stools or of material obtained by the proctoscope or at autopsy should reveal the presence of dysentery organisms. In dealing with outbreaks of bacillary dysentery it has been the experience of bacteriologists to recover the offending organism early from the stools of the children and adults involved. Yet in the many outbreaks of diarrhea of the newborn which we have followed, careful stool cultures and agglutination tests have to date not revealed dysentery bacilli to be the causative agent. Further, in keeping with the epidemiology of bacillary dysentery, if epidemic diarrhea of the newborn were due to B. dysenteriae, we should be able to demonstrate its spread to children and adults who have been in contact with the infected infants. But despite the fact that the latter are cared for subsequently in open pediatric wards or at home, no clinical or bacteriologic evidence has been obtained of spread of the disease to older infants or children or to the adults caring for the patients.

PATHOLOGY

Intestinal pathologic change is singularly meager in cases of epidemic diarrhea of the newborn. The conditions encountered most frequently are marked distention of the large and small intestines and surface hyperemia. Hemorrhage and ulceration are conspicuously absent, and there is only slight involvement of the mesenteric lymph nodes. Any further pathologic alterations of tissue are dependent on severity of infection and duration of illness and are of the types usually associated with rapid wasting diseases of early infancy. In babies dying after a more protracted clinical course, such conditions are present as bronchopneumonia, suppuration of the middle ear, cloudy swelling of the liver, spleen and kidneys and marantic thrombi of the cerebral vessels. The bronchopneumonia is an interstitial infiltration of round cells with some exudation into the alveoli of the lung. In general, however, no changes are found that are pathognomonically significant. The lack of pathologic change stands in sharp contrast to the well known pathologic picture in cases of bacillary dysentery in which death occurred. The intestinal lesions of bacillary dysentery are observed in the colon and in the lower portion of the ileum; they consist of swelling and edema of the mucosa and submucosa. Hemorrhage, necrosis, ulceration and pseudomembrane formation are prominent accompanying features, and mesenteric lymphadenopathy is marked.

DIFFERENTIAL DIAGNOSIS

During the initial stage of invasion, epidemic diarrhea of the newborn must be differentiated from simple gastrointestinal upsets due to such causes as overfeeding, improperly adjusted feeding mixtures or the indirect effects of drugs or laxatives given to the mothers of nursing

infants.[20a] In addition, two benign conditions simulating more serious diarrheal states of the newborn may cause confusion. The first is the so-called initial diarrhea of the newborn, in which the stools increase in frequency at the end of the second week of life and are loose and slimy, with many curds. Grulee and Bonar [21] have expressed the opinion that in many instances this diarrheal disturbance may be considered physiologic and that it is due probably to irritation of the intestinal mucosa by food, to the initial invasion of the alimentary tract by bacteria or to both. The second condition is the prandial diarrhea of infancy occurring at the time of nursing; Rodriquez [22] stated that it usually occurs in hyperspastic infants.

Of interest in differentiation of the disorder during the toxic stage is the relation of the diarrhea to parenteral disease. In addition to the laboratory criteria already noted, the mode of onset of epidemic diarrhea of the newborn, the absence of early fever and the lack of blood and of mucus in the stools serve to differentiate the disorder from bacillary dysentery, as well as from other primary and secondary diarrheal disorders of infants. The latter are acute in onset; temperature reactions and signs of gastrointestinal upset are early manifestations. Blood and mucus in the stools are prominent. In cases in which otitic and pulmonary complications are present, diarrhea may be considered a secondary disturbance. However, a careful review of the case history with reference to the manner of onset of the disease and to the sequence of initial symptoms and signs will indicate that conditions of the ear and lung are late complications. Bronchopneumonia is usually terminal. As to involvement of the ear it is not our intention to reopen the recent controversy on the relation of infections of the middle ear and the effect of operative intervention to diarrheal disturbances in infancy. The problem has been adequately discussed in the literature; it is probably best summarized by the statement of Marriott, Hartman and Senn [23] that it is only when otitis media or mastoiditis is the direct cause of diarrhea that good results follow paracentesis or antrotomy. In the cases of epidemic diarrhea of the newborn that were observed by us,

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20a. Tyson, R. M.; Shrader, E. A., and Perlman, H.: Drugs Transmitted Through Breast Milk: I. Laxatives, J. Pediat. **11**:824 (Dec.) 1937. Kurt, N. T., and Hatcher, R. A.: Excretion of Drugs in Milk, Am. J. Dis. Child. **49**:900 (April) 1935.

21. Grulee, C. G., and Bonar, B. E.: The New-Born, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 1, chap. 42, p. 15.

22. Rodriquez, R. M. C.: Prandial Diarrhea in the Infant, Arch. españ. pediat. **20**:296-315 (May) 1936.

23. Marriott, W. M.; Hartman, A., and Senn, M. J. E.: Observations on the Nature and Treatment of Diarrhea and the Associated Systemic Disturbances, J. Pediat. **3**:181-191 (July) 1933.

surgical procedures for complications involving the ear did not appreciably alter the clinical course of the disease. When terminal septic stages occur, at times the disorder may be confused with septic conditions of the newborn, such as that caused by omphalitis or by infections of the skin. However, blood cultures and a carefully recorded history will readily afford differentiation.

PROGNOSIS AND TREATMENT

The prognosis in cases of epidemic diarrhea of the newborn is necessarily guarded. As has been indicated previously, the outcome will depend in great measure on several factors relating to severity of infection, type of baby affected and time of recognition and treatment of the disease. In general, the earlier the diagnosis is made and the sooner treatment is begun, the better the chance of recovery. When these are so delayed that marked dehydration and toxicosis ensue and the carbon dioxide-combining power of the blood is depressed to extremely low levels, the chance of recovery is slight. Involvement of the respiratory tract and otitic complications likewise adversely alter the prognosis. To date, the average case fatality rate is 47 per cent. Premature infants succumb most readily. Examination of tables 1 and 2 will show, for example, that of the 14 premature babies affected in these outbreaks, 13 died (table 1, cases 9, 11, 14, 15, 20, 29, 30; table 2, cases 1, 3, 12, 15, 32, 34).

As to treatment, it can only be strongly emphasized that to be successful any therapy (such as controlled periods of starvation, continuous infusions, transfusions and graded feedings) directed toward combating the intoxication must be begun early and carried out carefully. The results of belated therapy are singularly discouraging. The treatment of complicating features will vary, of course, according to the presenting indications.

SUMMARY

This report comprises a detailed discussion of the clinical picture of epidemic diarrhea of the newborn. It is based on our extensive experiences with the disorder in New York during the past four years. Typical outbreaks are analyzed, and case records are cited. The few epidemics of similar nature which have been reported in the literature are likewise considered in their bearing on the problem.

In attempting to clarify the clinical characteristics of epidemic diarrhea of the newborn, the fact is emphasized that recognition and differentiation of the disorder entail a thorough understanding of the fundamental conditions underlying and setting the stage for an outbreak. Hence, the clinical aspects are considered in intimate relation to the epidemiologic features which characterize the inception and mode of spread of the disorder.

Epidemic diarrhea of the newborn is a specific disease entity affecting mainly newborn infants from 2 to 14 days of age; the median age at onset is 7 days. The disease has a high incidence of morbidity and death. The average morbidity rate is 15.5 per cent, the mortality rate 7.3 per cent and the case fatality rate 47 per cent.[3] The disorder exhibits the characteristics of a highly virulent communicable disease.

The median period of incubation is six and one-half days; it may vary from two to twenty-one days, depending on the time of exposure to the illness. The stage of invasion is brief and is marked by prodromal symptoms such as loss of appetite, increased frequency of stools, arrest of gain in weight, listlessness, distention, normal temperature and occasional vomiting. The clinical course in cases of severe involvement then progresses rapidly to the toxic stage, in which the stools are very watery, yellow and acid in reaction, show little mucus and rarely contain blood. The symptomatic train of intense intestinal intoxication, namely, acidosis, coma and exsiccosis is soon evident in all its details. The temperature usually varies between 100 and 101 F., and early signs and symptoms of infection of the respiratory tract or of other parenteral disease are lacking. The complications of the disorder are mainly of otitic and pulmonary origin and are late manifestations. At times septic stages may intervene terminally. The duration of illness in cases in which the outcome is fatal varies from one to twenty-five days, with a median value of seven days. Recovery in cases of milder involvement takes place in from three to twenty-six days; the median is a little less than nine days.

The clinical and pathologic differentiation of the disorder is discussed with reference to other primary and secondary diarrheal disturbances of infants. The prognosis is exceedingly uncertain and is greatly influenced by factors relating to early diagnosis and treatment, severity of infection, occurrence of complicating features and the condition of the baby at the time of onset of the illness. Premature infants fare badly. At present, the treatment of the disease is highly unsatisfactory. The etiology of the disorder remains a problem subject to further investigation.

As viewed in its totality in conjunction with its epidemiologic characteristics, epidemic diarrhea of the newborn is a definite clinical syndrome which may be separated from the general group of diarrheal disorders of early infancy.

News and Comment

GENERAL

Physicians Certified by American Board of Pediatrics.—The following physicians have been certified by the American Board of Pediatrics since the last report:

Barbara Beattie, Littleton, N. H.; Bernard Benjamin, Brooklyn; Theodore Bennett, Boston; Morris Berke, Brooklyn; Robert S. Buol, New Britain, Conn.; Charles C. Chapple, Philadelphia; Ralph Weir Daffinee, Boston; John A. V. Davies, Boston; Charles H. Deichman, Morristown, N. J.; Geoffrey Winslow Esty, Westfield, N. J.; Harry E. Gerner, Jersey City, N. J.; Reginald A. Higgons, Port Chester, N. Y.; Manuel S. Hirshberg, Hartford, Conn.; Harold Jacobziner, New York; William Joseph Kelley, Boston; Milton Kurzrok, Brooklyn; Thomas M. Lamb, Brooklyn; John Langdon, Providence, R. I.; Spencer Ely Levin, Boston; William F. Matthews, Montclair, N. J.; Margaret Harper McKee, New York; Philip R. Miller, Brooklyn; Wallace J. Nichols, Boston; David Edward Overton, Hempstead, N. Y.; William R. Phillips, Elmira, N. Y.; Henry Rabnowitz, Springfield, Mass.; Elizabeth Kirk Rose, Philadelphia; Samuel Rubin, Philadelphia; Harry Benjamin Silver, Newark, N. J.; Clement A. Smith, Brookline, Mass.; D. C. Wharton Smith, Baltimore; Norman Smith, Brooklyn; Morris Steiner, Brooklyn; Henry Sycle Stern, Richmond, Va.; Benjamin Stoloff, Brooklyn; Max Tennis, Boston; A. Leonard Van Horn, Washington, D. C.; John Howell West, Easton, Pa.; L. Holland Whitney, Brooklyn; Herman Yannet, New Haven, Conn.; Carl Zelson, New York; Bernard Zuger, Brooklyn.

All took the examination. At this examination sixty-three applicants were examined; forty-two passed, two were conditioned in one subject, eleven failed for the first time and eight failed for the second time.

Abstracts from Current Literature

Anatomy and Physiology

ESTABLISHMENT OF THE DIURNAL TEMPERATURE CYCLE. N. KLEITMAN, S. TITELBAUM and H. HOFFMANN, Am. J. Physiol. **119**:48 (May) 1937.

During the first year of a child's life there is a gradual increase in the range of the body's temperature and in the regularity of the curve of the diurnal temperature. During the second year of life the adult type of curve becomes definitely established, the range temporarily exceeding that of the adult curve because of a lower minimal temperature. The important endogenous factor is the adaptation of the child's routine of existence to the twenty-four hour cycle of alternating day and night, with respect to wakefulness and sleep, activity and rest.

NOURSE, Cleveland.

A TOPOGRAPHIC AND ANATOMIC POINT OF THE TWELFTH INTERCOSTAL NERVE WITH REFERENCE TO THE INTERPRETATION OF THE LOCALIZING VALUE OF MCBURNEY'S POINT. A. BAUDET, Gaz. d. hôp. **110**:925 (July 21) 1937.

Dissecting the cadavers of 42 adults and 2 children, Baudet found that the twelfth intercostal nerve or a branch of it passes through a tendon canal, about 1 cm. long, formed by the tendon of the internal oblique abdominal muscle. It is found exactly at the middle of the line connecting the superior iliac spine with the umbilicus. In 2 cases it was placed below and outside, and in 7 cases above and inside of this point, but never farther than 1 cm.

Distention of the abdomen compresses the canal. The pain on pressure in appendicitis is explained by pressure on a pathologically sensitive nerve against a firm background, like the pain point of the external peroneal nerve against the neck of the fibula or of the point of emergence of the anterior costal nerve in intercostal neuralgia.

McBurney's point does not correspond to either end of the vermiform process in its usual location.

KAJDI, Baltimore.

Biochemistry; Bacteriology, and Pathology

ON THE DIFFERENCES IN ACTIVITY OF SERUM COMPLEMENT FROM VARIOUS ANIMAL SPECIES. E. W. SHRIGLEY and M. R. IRWIN, J. Immunol. **32**:281 (April) 1937.

In interesting experiments the authors studied, by means of bactericidal tests, the ability of complement from various animal species to activate the normal thermostable antibody for Brucella suis in the serums of various other animal species. Guinea pig complement would not activate the antibody in ox, rabbit or sheep serums. Ox complement activated the antibody in the heated serums of the rabbit and ox and only partly that in sheep serum. Sheep complement restored the activity in sheep, rabbit and ox serums. Thus, the complement from one animal species is not interchangeable with that from another in normal bactericidal reactions.

FOTHERGILL, Boston.

HEMOLYTIC STREPTOCOCCUS TOXINS AND ANTITOXINS: V. TITRATION BY THE FLOCCULATION REACTION. L. RANE and L. WYMAN, J. Immunol. **32**:321 (April) 1937.

In this communication the authors describe a technic for applying the Ramon flocculation reaction to the titration of scarlet fever toxin and antitoxin. If the

titration is to be successful, a very strong toxin must be used. Thus, a unit of antitoxin combines with about 60,000 skin test doses of toxin. The flocculating value of a weak toxin can be determined, however, by blending it with a strong toxin. The paper should be consulted for a description of the details of these standardization procedures.

FOTHERGILL, Boston.

ACTION OF PARA-AMINOPHENYLSULFAMINE ON MOLDS. E. FOURNEAU and others, Compt. rend. Soc. de biol. **122**:652, 1936.

To portions of a proper medium for the growth of molds were added different quantities of para-aminophenylsulfamine so that these portions contained this drug in the dilutions 1:100, 1:1,000 and 1:10,000, respectively. The molds studied, Aspergillus niger, Aspergillus janselmi, Aspergillus fumigatus and Lichtheimia italica, were all inhibited in growth (in vitro) as is, also, the streptococcus.

WAHL, Cleveland.

HEMOGLOBINOPHILIC BACTERIA PATHOGENIC TO MAN IN THE AIR PASSAGES OF A HEALTHY CAT. J. KREMSREITER, Arch. f. Hyg. **118**:97 (May) 1937.

The author reports the case of a man 42 years old who suffered a severe prolonged infection following a cat bite of his left wrist. A pure culture of a gram-negative hemoglobinophilic bacillus was obtained from the infected tissue. Later a nonhemolytic Staphylococcus albus and a nonhemolytic Streptococcus were isolated, but the predominating organism was the one found first. The same organism was recovered from the trachea and bronchi of the cat that bit him. The organism corresponded to one described as found in cats (Rivers and Bayne-Jones) and in ferrets (Kairies).

GLASER, Rochester, N. Y.

Metabolism; Infant Feeding; Milk and Other Foods

THE EFFECT OF BENZEDRINE SULFATE ON THE BASAL METABOLISM OF CHILDREN. MATTHEW MOLITCH and SAMUEL POLIAKOFF, Arch. Pediat. **54**:683 (Nov.) 1937.

The effect of benzedrine sulfate on the basal metabolic rate of 17 normal boys was studied. Three boys were studied at intervals of five hours for four days, during which time the dose was progressively increased. Fourteen were studied and the basal metabolic rate determined about two hours after the ingestion of 20 mg. of benzedrine sulfate.

Benzedrine sulfate in moderately high doses tends to increase the basal metabolic rate in children. Although the activity of the subject was carefully observed during the test, this increase might possibly have been due to an increased muscular tone or activity rather than to an increased oxidation as a direct stimulation of the cells.

ORR, Buffalo.

IMMATURITY OF THE ORGANISM AS A FACTOR DETERMINING THE FAVORABLE INFLUENCE OF LACTOSE ON THE UTILIZATION OF CALCIUM AND PHOSPHORUS. ROWLAND B. FRENCH and GEORGE R. COWGILL, J. Nutrition **14**:383 (Oct.) 1937.

In view of conflicting results reported by observers, the authors thought it possible that the maturity of the subject might play some role in the effect of lactose on calcium metabolism. Workers using mature animals had reported no effect, while a definite effect was often reported by those using immature animals.

After carefully controlled experiments on rats and dogs, the authors concluded that the degree of maturity played a definite role in the effect of lactose on the utilization of calcium.

MUNNS, Winnetka, Ill.

RETENTION OF IRON IN CHILDHOOD. J. H. HUTCHISON, Arch. Dis. Childhood **12**:305 (Oct.) 1935.

Observations on the retention of iron over long periods have been made in 4 nonanemic and 2 anemic children. The body is capable of retaining large amounts of iron. Only a small percentage of this iron is utilized for the synthesis of hemoglobin, even in those children who show severe anemia. The necessity for giving large doses of iron by mouth does not depend on poor absorption of iron by the intestine. No evidence was obtained that variations in gastric acidity influence the retention of iron. The suggestion is made that the iron stored in the liver is unavailable for the formation of hemoglobin, and that only iron which overflows from the liver into the circulation can be utilized for the formation of hemoglobin. Massive doses are necessary to effect this.

KELLY, Milwaukee.

THE MODIFICATION OF COW'S MILK FOR INFANT FEEDING. H. L. WALLACE, Tr. Edinburgh Obst. Soc., 1937, p. 102; in Edinburgh M. J., September 1937.

The author discusses the best substitutes for breast milk when it is not obtainable. He has made various observations of the curd in cow's milk as altered by boiling, citrating, acidifying, peptonizing, the addition of starch and drying. Dried milk is safest and most easily prepared and can be made to resemble human milk. It is too expensive to be within reach of the homes in which it is most needed.

NEFF, Kansas City, Mo.

INFANT DIETETICS IN THE CASA DE CUNA. DEMOFILO GONZALEZ, Rev. mex. de puericultura **7**:106 (Feb.-April.) 1937.

The author reviews the infant formulas used at the Casa de Cuna. Most of them are composed of evaporated milk, plain or with lactic acid added. The usual carbohydrates are used. Lemon juice is commonly used as an acidifier. He reviews the simple arithmetic used in calculating formulas.

HERRON, Monroe, La.

APPLE DIET FOR YOUNG INFANTS. K. HERZMANN, Kinderärztl. Praxis **9**:1 (Jan.) 1938.

After from twelve to twenty-four hours of starvation the infants were treated for dyspepsia by feeding apple pulp exclusively for at least one day. Herzmann suspends the apple pulp obtained from fresh apples in a mixture containing 2 parts of tea and 1 part of Ringer's solution and gives from 60 to 75 Gm. of the apple pulp per day. Treatment is continued with the addition of acidified milks. The results obtained were excellent. The age of the youngest infant treated was 9 days.

HEYMANN, Cleveland.

DEHYDRATING ACTION OF A DIET LOW IN CARBOHYDRATE. A. ADLERSBERG and O. PORGES, Klin. Wchnschr. **12**:1446 (July 8) 1933.

Carbohydrate has a water-retaining action, this storage of water taking place not in the blood but in the tissues, principally in the skin. A low intake of carbohydrate has a dehydrating effect. This action can be utilized therapeutically in edema and in lessening inflammatory exudate, such as the quantity of sputum in bronchiectasis.

SILVERMAN, Syracuse, N. Y.

LACTOFLAVINE IN HUMAN MILK. L. DOXIADES, Monatschr. f. Kinderh. **70**:369 (July) 1937.

In order to determine whether lactoflavine in the diet is excreted in human milk, Doxiades tried experiments on 4 wetnurses. Two of the wetnurses were given

three quarters of a liter of buttermilk. The other two were given 300 Gm. of liver daily. Both of these substances are rich in lactoflavine. The results show that three hours after a meal lactoflavine appears in the milk and increases for ten hours. It reaches its height in four days. There are some individual differences. The nurses not receiving these substances gave milk not containing lactoflavine.

GERSTLEY, Chicago.

ACID-BASE REGULATION BY DIET. DIENST, München. med. Wchnschr. **84**:812 (May 21) 1937.

The conditions arising from excessive injection of acid and from endogenous increase in the formation of acid as in diabetes, cardiac insufficiency and renal acidosis can be compensated by a highly basic diet. If this is not done the body loses alkali, and there is increased urinary excretion of sodium. With increasing depletion of the sodium reserve there is retention of acids in the body, which neutralize the tissue alkalis. As a result there is excretion of calcium salts in the urine. Potassium salts are retained in the body in an attempt to replace the calcium in the tissues and edema develops.

A diet poor in sodium and rich in calcium, with an excess of base, can correct the cause of the edema. A diet high in meat or the administration of potassium chloride, ammonium chloride, magnesium sulfate or calcium chloride has only a transient diuretic effect. Organic salts of potassium have as good a diuretic effect as a raw diet.

BRAHDY, Mt. Vernon, N. Y.

DIAGNOSIS OF TUBERCULOSIS IN CHILDREN BY MEANS OF SEROLOGIC REACTIONS. J. PROCHÁZKA and J. PÍSAŘOVIČOVÁ, Časop. lék. česk. **74**:1001 (Sept. 20) 1935.

After analyzing the results with the Meinicke, the Ballung-Haag-Niggemeyer and the Witebski-Klingenstein-Kuhn tests the authors feel that these tests are of little value in the diagnosis of tuberculosis in children under 14 years of age. A positive Meinicke reaction in the absence of syphilis is of some diagnostic value, but a positive reaction in a child is rare. A positive reaction to tuberculin in a child up to between 2 and 3 years is regarded as diagnostic of active tuberculosis.

STULIK, Chicago.

Vitamins; Avitaminoses

HYPERVITAMINOSIS-D. A. W. HUBBARD, Illinois M. J. **72**:253 (Sept.) 1937.

Reports on the use of massive doses of vitamin D prompted this review pertaining to possible vitamin D poisoning. Hubbard reviews the literature and discusses the possible injurious effects of incautious treatment with vitamin D by physicians and of its indiscriminate use by the laity.

BARBOUR, Peoria, Ill.

THE METABOLIC BACKGROUND OF RICKETS. R. GUBNER, New England J. Med. **216**:879 (May 20) 1937.

The multitudinous studies on the causation of rickets are thoroughly discussed from the standpoint of an extensive bibliography. Gubner feels that rickets is considered to be a disease resulting from a disturbance in calcium and phosphorus metabolism. Deficiency of vitamin D results in diminished intestinal retention of phosphorus, which carries out calcium as insoluble calcium phosphate. In an attempt to preserve homeostasis of serum calcium the parathyroid glands are driven to increased functional activity releasing calcium from the skeletal reservoirs. The osteoporosis acts as a stimulus to regeneration, with increased osteoblastic activity, especially at the metaphyses of the long bones, where growth is normally greatest and where resorption of bone minerals by parathormone is most active.

Owing to the disturbed mineral balance, calcification is not wholly successful, and the characteristic features of rickets—presence of abundant osteoid matrix and defective calcification—are produced.

In addition to the bony changes, there is a general metabolic disturbance, which is manifest chiefly as muscular weakness. This is due to depletion of body phosphate which interferes with carbohydrate metabolism. It is possible that loss of phosphate may also impair fat and creatine metabolism.

GENGENBACH, Denver.

THE USE OF A DARK ADAPTATION TECHNIQUE (BIOPHOTOMETER) IN THE MEASUREMENT OF VITAMIN A DEFICIENCY IN CHILDREN. CARROLL E. PALMER and H. BLUMBERG, Pub. Health Rep. **52**:1403 (Oct. 8) 1937.

The dark adaption test with the biophotometer was used in a survey of 585 elementary school children in Maryland and the District of Columbia. It was found that little dependence could be placed on a single test for each child, and significant variance occurred in the results of successive tests. The results of the survey gave no evidence justifying the belief that vitamin A deficiency was prevalent in this group of children. This test does not appear to be accurate or reliable for detecting mild degrees of vitamin A deficiency in a routine survey of school children.

SANFORD, Chicago.

RICKETS IN EARLY INFANCY IN MONTEVIDEO. A. CARRAU and H. C. BAZZANO, Arch. de pediat. d. Uruguay **8**:428 (July) 1937.

Rickets is present in from 15 to 18 per cent of infants in the hospitals of Montevideo, Uruguay. The age at which it occurs ranges between 3 months and 2½ years. No time of the year is distinguished by greater frequency of this disease.

Congenital syphilis is not a cause of rickets, but the subjects of this disease are often the offspring of tuberculous parents.

Most of the children present light forms. Prolonged or relapsing rickets is rare.

The roentgen pictures are typical and resemble those observed in central Europe.

Practically all the children recover completely.

The avitaminoses A and C are rare in the hospital material. Keratomalacia was encountered in 1 of 3,000 infants and scurvy in 3.

SCHLUTZ, Chicago.

THE RELATION OF LIVER FUNCTION TO VITAMIN C. Y. HIRATA, Orient. J. Dis. Infants **21**:39 (May) 1937.

In acute and chronic chloroform poisoning in rabbits Hirata found a definite reduction in the vitamin C content of the liver. When a large quantity of vitamin C was administered to these animals it prevented such functional disturbances of the liver as decrease in the hepatic glycogen, glycogenetic function of the liver and hepatic degeneration. Administration of vitamin C, therefore, stimulates or regulates the function of the liver, especially with reference to intoxication.

KATO, Chicago.

Hygiene; Growth and Nutrition; Public Health

NUTRITION PROBLEMS IN EDUCATION. J. S. MCLESTER, J. A. M. A. **109**:838 (Sept. 11) 1937.

In the nutritional program of public schools there should be included measures for the detection of individual cases of nutritional failure and for the improvement of the nutritional status of the entire student body. This program should be broadly educational.

BONAR, Salt Lake City.

LIGHT IN THE SCHOOLROOM. E. JACKSON, J. A. M. A. **109**:841 (Sept. 11) 1937.

More than good light in the schoolroom is needed. Adequate light is required for all children. This cannot be attained until teachers, parents and pupils understand what is good light. When these essentials have been mastered, school authorities, architects and financiers still will need instruction regarding good lighting.

BONAR, Salt Lake City.

HEALTH EDUCATION AND HEALTH SERVICES IN SCHOOLS. J. F. ROGERS, J. A. M. A. **109**:842 (Sept. 11) 1937.

The teacher is an important agent in the school health service, in that she is the daily examiner. The parent needs to be taken into the examiner's confidence, so that he may learn something himself of the results of his own work. To attempt to do too much is not educational and is a waste of time. More conservatism in making conclusions is needed. The family physician should be made the periodic examiner if possible, and he should reciprocate by providing treatment for indigent patients. The school director of health should be educated to make the most of his opportunities for both service and study.

BONAR, Salt Lake City.

PREVENTIVE PEDIATRICS. H. CASPARIS, South. M. J. **30**:746 (July) 1937.

Casparis recommends that every child entering school should have a sufficiently comprehensive health examination (mental and physical) to enable his supervisors to determine where he should be placed in school and how he should be taught if he is to get the best results out of the valuable facilities which the school provides for his education. Under such requirements the parents would in his early childhood become concerned about his mental and physical health just as they become concerned about his going to school when he is 6 years old or earlier. Likewise, physicians, knowing that the chief burden of the care of the child's health during the first six years rests on them and knowing the necessity for a comprehensive examination of the child before he enters school, could be more easily stimulated and educated to assume this responsibility, with a higher level of accomplishment, than is observable at present.

SCHLUTZ, Chicago.

Prematurity and Congenital Deformities

THE RESPONSIBILITY OF THE OFFICIAL AGENCY IN MATERNAL AND CHILD HEALTH. J. WARREN BELL, Nebraska M. J. **22**:325 (Sept.) 1937.

Bell visited ten European countries and found the statistics of some nations on the health of mothers and children were absolutely unreliable. On the other hand, those from the secretariat of the Health Organizations of the League of Nations were accurately kept and conservatively handled. In considering the problems of health in the forty-eight states of the United States, it is necessary to remember that the activities of departments of health have been frequently confused and sometimes entirely swamped and submerged by the rapid mushroom-like development of welfare organizations. Departments of health must face frankly the social aspect of the problems without losing sight of the primary position which health holds in modern society.

The Nebraska Division of Maternal and Child Health is making available literature on the care and the health of the expectant mother and her child. It is seeking to arouse public interest through the press and other agencies and organizations. In those counties where the mortality of mothers and infants has been significantly high, conferences are held with physicians. In some counties local programs have been established. With the aid of nineteen physicians, "refresher" courses have been held in various parts of the state. Where local

initiative has been displayed, the attendance has been good. Approximately 6 speakers have appeared in each of eight regions. Provision is made for local study of special problems in limited areas. In two counties public health nurses have been made available. These nurses visit expectant mothers and teach the reasons for prenatal care and the importance of nutrition, immunization and the development of a family pattern of living compatible with a stable personality in the young child. Dental hygiene is, by means of films and lectures, discussed with various groups. The program does not profess to go beyond the confines of education in the health of mothers and children. The Nebraska State Medical Association has and is taking the initiative in studying the factors contributing to mortality of mothers and infants.

HAMILTON, Omaha.

THE CAUSES OF STILLBIRTHS. E. C. DUNHAM and E. C. TANDY, South. M. J. **30**:643 (June) 1937.

On the basis of their preliminary analysis, Dunham and Tandy believe that in the case of stillbirths an assignment of cause can be made satisfactorily only by taking into consideration not only the conditions found in the fetus that might account for its death but also the complications of the mother's pregnancy, labor and delivery, as well as the time of the death of the fetus.

In a total group of 2,000 stillborn infants they found that in only 18 per cent was no cause determined. In 9 per cent a fetal cause was determined, but no maternal cause. In 33 per cent a maternal cause was determined, but no fetal cause. In 40 per cent both fetal and maternal causes were determined.

SCHLUTZ, Chicago.

A CASE OF PARTIAL CHORIONIC DEGENERATION OF THE PLACENTA WITH A PREMATURE LIVE FOETUS. K. M. MASANI, J. Obst. & Gynaec. Brit. Emp. **44**: 340 (April) 1937.

A case is reported in which an infant weighing 2 pounds (907 Gm.) was delivered and lived two days. The placenta showed a sharply demarcated area of degeneration, despite which the fetus was able to continue an intrauterine existence for a moderate length of time.

ADAIR and POTTER, Chicago.

INCIDENCE OF HUMAN MALFORMATIONS AND THE SIGNIFICANCE OF CHANGES IN THE MATERNAL ENVIRONMENT IN THEIR CAUSATION. P. MALPAS, J. Obst. & Gynaec. Brit. Emp. **44**:434 (June) 1937.

The incidence of 2.1 for malformations occurring among 13,964 newborn infants in the Liverpool Maternity Hospital is divided into 1.065 for cerebrospinal anomalies and 1.04 for all other types. Investigation of these cases showed no parental consanguinity. Anencephalus, hydrocephalus, congenital cardiac disease, mongolian idiocy, possibly harelip and cleft palate are more frequent with the later maternal age groups. Other malformations show no definite relation to maternal age. Parity has little relation to malformations except for hypospadias. This is much more common with primiparas than with multiparas.

Malpas believes that all malformations, regardless of type, have as a common etiologic basis abnormal uterine environment in the early weeks of gestation and that the type of malformation is totally unrelated to genetic constitution.

ADAIR and POTTER, Chicago.

AMELIA. P. LEREBOULLET, A. HOVELACQUE and H. EVRARD, Arch. de méd. d. enf. **40**:617 (Oct.) 1937.

The total congenital absence of one or more limbs represents the most marked degree of ectromelia. Relatively rare, it has received little consideration from an anatomic point of view. Two cases are reported exhaustively by the authors.

One of the subjects, a girl aged 11 years, had been under close observation for almost two years. Both arms and both legs were absent, and the development of the shoulder girdles was rudimentary. When she died from coincident pneumonia and nephritis at the age of 13, systematic studies were conducted on the osseous, muscular, vascular and nervous elements involved. The second subject, also a girl, came under medical supervision at the age of 2 or 3 months, when dying. A history could not be secured. A complete autopsy was performed. The infant had total amelia, with mutilations similar to those of the first patient.

In their comment on this congenital defect the writers discountenance the theory of intrauterine amputation by fibrous bands.

AMESSE, Denver.

HEREDITARY CRANIOFACIAL DYSOSTOSIS AND TOWER HEAD. E. REISER, Med. Klin. **33**:1229 (Sept. 10) 1937.

A case is reported. Reiser thinks that dysostosis craniofacialis hereditaria is the full expression of the symptom complex of tower head. Other types of tower head can be regarded as formes frustes. The facial expression is froglike and the eyes widely separated, and there are exophthalmos and depression of the bridge of the nose. Pathologically the condition is characterized by an abnormally small base of the skull and an increase in its vertical dimensions. In case cerebral growth cannot be accommodated by growth of the skull (evidenced by increase in digital markings roentgenologically) symptoms of increased intracranial pressure may appear. Downward growth of the brain in the occipital region may produce angulation and partial obstruction of the aqueduct of Sylvius and lead to hydrocephalus. Reiser thinks that, in addition to the hereditary factor, limited intrauterine space may be a factor in inhibiting lateral growth of the skull.

SIEMSEN, Chicago.

ANENCEPHALY. S. HANSEN, Hospitalstid. **80**:469 (April 27) 1937.

Hansen has collected 80 cases of anencephaly from Danish maternity wards. In 2 of the cases the infants lived for a short time after birth. Sixty-nine of the infants were female; 11, male. Twenty-five were born at full term. The primary cause of the anencephaly is considered to be an increased secretion of cerebrospinal fluid, through which the skull is expanded at its thinnest part as if it had been blown up. In less severe cases of hypersecretion of this fluid, hydrocephalus or spina bifida develops.

WALLGREN, Göteborg, Sweden.

Newborn

SUPPURATIVE PAROTITIS OF THE NEW-BORN. HARRY BLOCH and B. L. PACELLA, Arch. Pediat. **54**:681 (Nov.) 1937.

Two cases are reported.

ORR, Buffalo.

CHEMICAL CONJUNCTIVITIS OF THE NEWBORN: ITS CAUSE, PREVENTION, AND TREATMENT. LEWIS PELLMAN GLOVER, Pennsylvania M. J. **40**:1035 (Sept.) 1937.

Chemical conjunctivitis of the newborn is an irritation of the eyes which begins between the second and the tenth day after delivery and is the result of the use of some silver preparation to prevent ophthalmia neonatorum. In spite of the use of the silver preparation, infection does take place by the gonococcus in a few cases. In many more, however, there is present what has been termed a nonspecific infection; on examination the smears prove to be free from bacteria, although there are varying amounts of pus. This pus, together with the swelling which is sometimes present, has led many physicians to entertain the mistaken idea that the infection is gonorrheal.

The author demonstrates that this condition is due to the use of old solutions of silver or the silver salts. To avoid this chemical irritation all solutions must be made up fresh each week, care being taken that the bottle and the cork are cleansed each time.

LOGUE, Williamsport, Pa.

ETIOLOGY AND PATHOGENESIS OF BUHL'S DISEASE. E. CRACIUN, H. SLOBOZIANU and A. URSU, Arch. de méd. d. enf. **40**:636 (Oct.) 1937.

During the long period of intrauterine life the embryo and later the fetus is exposed to numerous toxic infections which determine death of the products of conception, prematurity and congenital debility or disease. These first months must receive more pathologic study if certain problems of prime importance are to be solved. Unquestionably, the transmission of bacteria from an apparently healthy mother to the fetus frequently occurs; some of these organisms are saprophytic for both, while others may be saprophytic for the mother but pathogenic for the infant. The authors report an instance in which twins suffered from congenital fetal peritonitis. Bacillus faecalis alcaligenes was recovered in pure culture, although the mother had not been ill either before or after accouchement.

Another organism which may readily assume a pathogenic status in the fetus is the colibacillus, which has frequently been shown to be the source of grave septicemia and of the fatty degeneration which characterizes Buhl's disease. A case of that condition is reported in full.

AMESSE, Denver.

SEQUELS OF ICTERUS NEONATORUM GRAVIS. E. BURGHARD and H. SCHLEUSSING, Klin. Wchnschr. **12**:1526 (July 8) 1933.

This is the report of an infant in whom icterus had practically disappeared on the eleventh day except for the scleras. There developed, however, encephalitic symptoms with opisthotonos, dulness of the sensorium, profuse sweating and parkinsonism. The child died at 5 months. They found the yellowish discoloration in certain portions of the brain (corpus Luysii, cornu ammonis).

SILVERMAN, Syracuse, N. Y.

ON THE OXYGEN DISSOCIATION CURVE OF HEMOGLOBIN IN THE UMBILICAL BLOOD OF NEW-BORNS: III. FURTHER STUDIES ON THE GASES IN THE UMBILICAL BLOOD. M. NOGUCHI, Jap. J. Obst. & Gynec. **20**:358 (July) 1937.

The oxygen dissociation curve of blood from the umbilical cord was studied in 5 infants and found to agree entirely with the dissociation curve of blood from normal adults.

ADAIR and POTTER, Chicago.

ERYTHROBLASTOSIS NEONATORUM FAMILIARIS. L. SALOMONSEN, Norsk mag. f. lægevidensk. **98**:765 (June) 1937.

The physiologic erythroblastosis that is found in every newborn infant during the first week of life does not exceed that represented by a count of 0.5 per thousand red blood corpuscles. In some pathologic conditions the proportion of erythroblasts may be much higher. Salomonsen cites 3 such cases. The first was that of a newborn baby with congenital hydrops who lived for six hours. A blood count showed the proportion of erythroblasts to be 1.6 per hundred of different sorts of nucleated red corpuscles. The hemoglobin content was 81 per cent; the red blood corpuscle count was 3,765,000 and the white cell count 61,800, with many immature cells. The liver and spleen were enlarged. The incidence of congenital hydrops was considered to be about 0.3 per thousand births. The second case was one of icterus congenitus gravis. It occurred in a boy whose weight at birth was 4,100 Gm. Twelve hours after birth jaundice was noted, which rapidly increased, while the skin became more and more pale. The spleen and

liver were enlarged. The blood was examined on the ninth day: The hemoglobin content was 30 per cent. The red blood corpuscle count was 1,270,000; the erythroblast count, 12.3 per thousand red corpuscles; the white blood cell count, 15,600, many of them immature. After blood transfusions there was rapid recovery, and when the infant was 3½ weeks old the erythroblasts had disappeared. Later on, symptoms of cerebral involvement developed. The third case had previously been reported by Dedichen in 1935. In this case the erythroblasts amounted to only 2.1 per thousand red corpuscles.

WALLGREN, Göteborg, Sweden.

Acute Contagious Diseases

SCARLET FEVER. JEAN V. COOKE, Ann. Int. Med. **11**:485 (Sept.) 1937.

In a lucid and concise article Cooke outlines the modern conception of scarlet fever.

He admits that all evidence points to the hemolytic streptococcus as the cause of scarlet fever, but he believes that any strain of streptococcus is capable of producing the disease, depending on whether the organism is capable of producing the erythrogenic toxin to which patients with classic scarlet fever are susceptible.

It is doubtful whether scarlet fever is a distinct disease entity. Clinical scarlet fever is probably a toxic syndrome that accompanies infection with hemolytic streptococcus in certain susceptible persons.

The manifestations of the disease can be separated into two components, a septic component, which includes the sore throat and the direct extension of the infection to adjacent tissues, and a toxic component, which includes the rash, vomiting, adenopathy and fever. Immunologically these two phases are distinct. The toxic manifestations either are caused by an exotoxin or depend on an allergic state of the tissues produced by preceding streptococcic infections, the latter explanation being the more likely.

READING, Galveston.

DIFFERENTIAL DIAGNOSIS OF EPIDEMIC MENINGITIS FROM OTHER FORMS OF MENINGEAL IRRITATIONS. J. A. TOOMEY, Arch. Pediat. **54**:381 (July) 1937.

It is believed that meningeal infections due to bacteria may be (*a*) acute and primary, starting first in the meninges (a belief to which the author does not subscribe), (*b*) acute and secondary to an infection with a homologous organism or (*c*) chronic and secondary to some acute or chronic infection elsewhere in the body. Meningitis is probably always a hematogenous infection secondary to an acute or chronic infection elsewhere rather than a direct infection through the cribriform plate of the ethmoid or by way of the lymphatics or blood vessels, although infection of the meninges in the latter way is possible.

There are some well regarded points that aid in a tentative diagnosis of the type of meningitis that is present, to be confirmed later by a lumbar puncture.

The author excludes those types of epidemic meningitis which cause death within from twenty-four to forty-eight hours after the onset. They are usually not diagnosed except during an epidemic.

Five clinical findings are described which are suggestive of epidemic meningitis, though not necessarily pathognomonic of the disease:

1. Onset. In nearly all cases epidemic meningitis starts suddenly. Sudden severe headache, nausea or vomiting and signs of meningeal irritation in a person previously well are suggestive of epidemic meningitis.

2. Appearance of the patient. The patient is usually wide awake, well oriented and keenly aware of his surroundings.

3. Duration and mortality. Excluding patients with profound toxicity who die within from forty-eight to seventy-two hours, patients with epidemic meningitis may not die, or the disease may run a considerable length of time before death occurs. For practical purposes the mortality in epidemic meningitis is low when

compared with that from any other type of acute purulent meningitis. All other types are about 100 per cent fatal. The author states that this opinion may have to be modified in view of recent recoveries from streptococcic meningitis following the use of sulfanilamide.

4. Temperature and pulse. A rapidly rising temperature, reaching 104 F., and a rise in pulse rate are usual in meningococcic infection.

5. Neurologic signs. The persistence of neurologic signs is common to all forms of purulent meningitis in contradistinction to the bizarreness of neurologic reactions in tuberculous meningitis.

The impressions gained from the clinical findings can usually be confirmed by the findings obtained from a thorough examination of the spinal fluid.

Brief summaries of twenty-three case histories are submitted.

ORR, Buffalo.

THE VALUE OF CONVALESCENT BLOOD AND IMMUNE ADULT BLOOD IN THE CONTROL OF MEASLES. CLARENCE M. HYLAND and LUCILE RUSSELL ANDERSON, Arch. Pediat. **54**:633 (Nov.) 1937.

The authors have reviewed the medical literature of the English-speaking countries with regard to the use of convalescent and immune adult blood in the control of measles. The material is arranged under five headings as follows.

1. *Use of Convalescent Serum or Convalescent Whole Blood for Prophylaxis in Institutional Contacts.*—A prophylactic injection of convalescent serum or convalescent whole blood was given to 3,610 persons, of whom 83.9 per cent escaped measles; modified measles developed in 13.4 per cent, and 2.6 per cent contracted typical measles. There were 626 controls who did not receive prophylaxis; typical measles developed in 53.5 per cent.

2. *Use of Immune Adult Serum or Adult Whole Blood for Prophylaxis in Institutional Contacts.*—Immune adult serum or whole blood was given to 618 persons after exposure to measles; of these 60.1 per cent escaped infection, 21.8 per cent had modified measles and 18 per cent contracted typical measles. Of 127 controls who were not treated with serum 59 per cent contracted typical measles.

3. *Use of Convalescent Serum or Convalescent Whole Blood for Prophylaxis in Home Contacts.*—Convalescent serum or whole blood was given to 2,334 persons who had come in contact with measles at home; of these 67.7 per cent were protected, 28.5 per cent had modified measles and 3.6 per cent contracted typical measles. In the control series of 193 subjects who had not received prophylaxis, measles developed in 80.3 per cent.

4. *Use of Immune Adult Serum or Adult Whole Blood for Prophylaxis in Home Contacts.*—Immune adult serum or whole blood was given to 774 persons, of whom 47.1 per cent were protected, 37 per cent had modified measles and 15.8 per cent had typical measles. Measles developed in 82.1 per cent of the 191 controls who received no serum. The results obtained from the use of immune adult serum and whole blood were not so favorable as those obtained from the use of convalescent serum and whole blood. Of all the persons who received immune serum or whole blood, 83.2 per cent were protected from measles or had a modified form of the disease, while in the groups receiving convalescent blood or serum 95.3 per cent were protected from the disease or had it in a modified form.

5. *Therapeutic Use of Convalescent Serum or Convalescent Whole Blood.*—There were 45 cases found on record in which the treatment was used. In 38 there appeared to have been benefit; in 2 the disease was moderately severe, and in 5 the condition was not influenced. The authors are of the opinion that there may be value in the use of convalescent serum or whole blood in the treatment of measles, provided large doses are administered.

ORR, Buffalo.

SCARLET FEVER AND ITS COMPLICATIONS. E. H. QUANDT, Illinois M. J. **72**:323 (Oct.) 1937.

In a statistical study of 783 cases of scarlet fever in school children in Rockford, Ill., one year after an epidemic, Quandt found that in 24 per cent of all cases one or more complications or sequelae had developed. Infection of the middle ear was the most common immediate complication. Cardiac damage was the most common permanent complication. The school with the highest percentage of immune children prior to the epidemic had the lowest incidence of the disease.

BARBOUR, Peoria, Ill.

ACTIVE IMMUNIZATION OF TUBERCULOUS CHILDREN AGAINST WHOOPING COUGH WITH SAUER'S VACCINE. M. SIEGEL and E. W. GOLDBERGER, J. A. M. A. **109**:1088 (Oct. 2) 1937.

Sauer's authorized commercial whooping cough vaccine in a dose of 80,000,000,000 bacilli did not seem to prevent the appearance of the disease in a group of vaccinated tuberculous children exposed to whooping cough. However, as a whole, the symptoms of the vaccinated children seemed milder and of shorter duration than those of unvaccinated children.

BONAR, Salt Lake City.

UNSUCCESSFUL ATTEMPTS TO CULTIVATE THE VIRUS OF EPIDEMIC POLIOMYELITIS IN VARIOUS LIVING TISSUE MEDIUMS. C. KAST and J. A. KOLMER, J. Infect. Dis. **61**:60 (July-Aug.) 1937.

Kast and Kolmer report that they have not been able to cultivate the virus of infantile paralysis with methods based on principles successfully employed in the cultivation of other viruses. That is to say, their attempts to cultivate the virus in a form virulent for Macacus rhesus on intracerebral inoculation have been unsuccessful. There is the probability, however, of cultivation with loss of virulence, and this possibility is being investigated.

TOOMEY, Cleveland.

ATTEMPTS TO TRANSMIT EPIDEMIC POLIOMYELITIS TO RABBITS, GUINEA PIGS, RATS, MICE, CHICKENS AND FERRETS WITH AND WITHOUT DEPRESSION BY X-RAYS. J. A. KOLMER, A. M. RULE and M. WERNER, J. Infect. Dis. **61**:63 (July-Aug.) 1937.

Young rabbits were not successfully infected with a virulent remote monkey passage strain of poliomyelitis virus by intracerebral, intracisternal, intravenous, intraperitoneal or intranasal inoculation so far as the production of clinical evidences and lesions of the spinal cord was concerned. Adult rabbits were not successfully infected by intracerebral inoculation during or after depression by roentgen rays.

Ferrets were not successfully infected by intracerebral or intraperitoneal inoculation nor by intracerebral inoculation during or after depression by roentgen rays.

Young guinea-pigs were resistant to intracerebral, intravenous and intraperitoneal inoculation of the virus and likewise to intracerebral inoculation during or after depression by roentgen rays.

White mice were apparently resistant to infection by intracerebral and intraperitoneal inoculation. Preliminary intracerebral injection of sterile starch did not result in demonstrable localization of virus injected intraperitoneally.

Chickens were not successfully infected by intracerebral inoculation of virus.

Some mice given repeated intraperitoneal injections of virus, as well as young rabbits inoculated intravenously, succumbed without demonstrable lesions of the spinal cord or clinical evidences of poliomyelitis, but the study is being continued to determine the possibility of infection of other tissues and especially of the organs of the reticulo-endothelial system.

TOOMEY, Cleveland.

THE VALUE OF CONVALESCENT SERUM IN THE ACUTE CONTAGIOUS DISEASES. C. M. HYLAND, Nebraska M. J. **22**:342 (Sept.) 1937.

The value of convalescent serum is not yet as generally appreciated as it should be. This is partly because of the difficulty of securing the serum in a sufficient amount. A few of the larger medical centers have undertaken to collect, prepare, store and distribute the serum as needed.

Measles is recognized as a serious disease, particularly in children suffering from malnutrition or some chronic infection. In the author's study of 423 subjects with whom patients came in contact in the home, all of whom were subjected to direct exposure to measles, 97.7 per cent were benefited by the prophylactic injection of convalescent serum. Illness was prevented in 72.5 per cent and modified in 25.2 per cent.

Of 102 subjects who were exposed to scarlet fever at home and who received prophylactic injections of convalescent serum, 4 contracted scarlet fever. In 3 of these the attack was mild. In the author's opinion, convalescent serum not only influences the course of the disease but lowers the incidence of complications. Early and adequate dosage is important.

For chickenpox, mumps and whooping cough the use of convalescent serum is permissible and may be of some use.

Opinions are still conflicting with regard to the value of convalescent serum in the treatment of poliomyelitis. Jensen is quoted as saying that in serum from patients in whom the disease produced paralysis there are from 1,000 to 2,000 protective doses per cubic centimeter, that serum from nonparalytic patients contains approximately 8,000 protective doses per cubic centimeter, and that serum from patients who sustained an abortive attack of poliomyelitis attained the astonishingly high figure of approximately 150,000 protective doses per cubic centimeter.

The secret of any serum therapy is early and adequate dosage.

HAMILTON, Omaha.

A MILK-BORNE EPIDEMIC OF SCARLET FEVER. Pub. Health Rep. **52**:1013 (July 23) 1937.

The epidemic occurred in Chautauqua, N. Y., and eleven persons had the disease. All had drunk raw milk sold without a permit by a local dairyman. The first patient was a student boarder in the dairyman's home, who was in no way connected with the dairy. The dairyman had an infection on his thumb which may have been the means of carrying the infection to the milk, as he did all his own bottling, capping and milking.

SANFORD, Chicago.

CURRENT PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **52**:1207 (Sept. 3) 1937.

For the period from July 18 to Aug. 14, 1937, the number of cases of poliomyelitis rose to 1,589, over double that of the previous four weeks. This epidemic was confined to the South Central and the East North Central region. The incidence of measles, smallpox, meningitis and typhoid was slightly in excess of normal, while that of scarlet fever, diphtheria and influenza was lower. The average mortality was 10.2 per thousand. This is about a median for the last four years.

SANFORD, Chicago.

GENERALIZED VACCINIA. J. D. ROLLESTON, Brit. J. Child. Dis. **34**:187 (July-Sept.) 1937.

A 7 month old boy was vaccinated shortly after an attack of varicella, and generalized vaccinia developed. Rolleston stated that generalized vaccinia is rare at any age and admitted that the case he reported was the first of its kind that he

had observed in over thirty-five years' practice. As a rule, the prognosis is good. The condition is likely to be serious and even fatal only when it supervenes on a preexisting dermatosis, especially eczema, seborrheic dermatitis or impetigo.

According to modern views, generalized vaccinia is a hematogenous outcrop of the vaccine virus rather than a consequence of external inoculation.

LANGMANN, New York.

ANTI-DIPHTHERIA IMMUNISATION. D. F. HANLY, Irish J. M. Sc., September 1937, p. 578.

Difficulty was observed in getting the children and the parents to cooperate. Toxoid-antitoxin mixtures were used first, a full course comprising three injections into the deltoid muscles. The children of preschool age had no reactions, but older patients did. Schick tests showed 96 per cent immunization after injections of toxoid-antitoxin. A single injection of alum-precipitated toxoid was later used, to eliminate the possibility that some subjects would not complete the course. In a test group, 45 of 46 children were made to respond negatively to the Schick test by one injection of alum-precipitated toxoid. Estimations of the antigen content of the blood were made in this group; these showed that the immunity conferred varied from 0.04 to 25 units per cubic centimeter. With alum-precipitated toxoid, 89 reactions occurred in 38,303 cases; some patients had local reactions, some local abscesses and a few generalized reactions.

In the epidemic of diphtheria which followed, diphtheria was contracted by 0.2 per cent of those who had been inoculated with toxoid-antitoxin mixture, 0.26 per cent who had been inoculated with toxoid-antitoxin floccules and 0.19 per cent who were immunized with alum-precipitated toxoid. Five patients who had received alum-precipitated toxoid, one who had received toxoid-antitoxin mixture and one who had received toxoid-antitoxin floccules died.

SNELLING, Toronto, Canada.

THE BACTERIOLOGICAL DIAGNOSIS OF WHOOPING-COUGH. EDITH A. STRAKER and J. S. WESTWATER, Lancet **2**:565 (Sept. 4) 1937.

Of 125 cases of whooping cough in which examination was made in the catarrhal or the early spasmodic stage, the coughplate test gave positive results in 98 (78.4 per cent). The Danish modification of the Bordet-Gengou formula with 50 per cent fresh defibrinated or oxalated horse blood was used.

LANGMANN, New York.

IMMUNISING FRACTIONS ISOLATED FROM HAEMOPHILUS PERTUSSIS. J. C. CRUICKSHANK and G. G. FREEMAN, Lancet **2**:567 (Sept. 4) 1937.

An antigenically active fraction was obtained from Haemophilus pertussis which appeared to possess an immunizing potency, as tested in mice, equal to that of whole bacterial cells derived from a virulent phase I strain.

LANGMANN, New York.

ROSEOLA INFANTUM—"ROSE-RASH OF INFANTS." M. WITKIN, South African M. J. **11**:499 (July 24) 1934.

Witkin discusses briefly the clinical picture of roseola infantum. He has seen sixteen cases of this disease in the last twenty-two months and is convinced that it is as common as any of the other exanthems.

GONCE, Madison, Wis.

SIMULTANEOUS DISAPPEARANCE OF WARTS AND THE SCABS OF CHICKENPOX. A. IANCOU, Arch. de méd. d. enf. **40**:443 (July) 1937.

Numerous warts affecting the hands and the perioral region of a child aged 5 disappeared with convalescence from varicella. The invasion was especially severe, and the temperature reached 39 C. (102.2 F.), but there were no complications. It

was noted that the largest of the verrucous growths disappeared first, followed by those of medium size and finally by the most minute; in other words, they fell in the order of their original appearance. It was logical to assume that the medication exhibited during the febrile stage might have been responsible for this parallel evolution; this consisted of the usual antipyretic therapy and external application of a powder composed of bismuth subgallate, zinc oxide and talcum. The author discusses therapy by suggestion, as advanced by L. Brocquad and other European clinicians, but discards this in favor of vaccinotherapy provoked by the onset of chickenpox, since this infection involves the same plane of the integument as the warty excrescences.

AMESSE, Denver.

POSTMORBILLOUS GANGRENE: REPORT OF A CASE. S. BARTSOCAS and GRIGORIOU, Arch. de méd. d. enf. **40**:585 (Sept.) 1937.

Gangrene following an invasion of measles is now so rare that the authors feel compelled to report observation of it.

A girl of 2 years, whose family and personal history were irrelevant, presented the features of a moderately severe attack of measles. When convalescence was well established, she suddenly complained of severe pain in the right foot. Examination showed the skin to be blanched and cold; it was exquisitely tender, and the nails were bluish. The temperature at the time of the examination was 104 F. Within twenty-four hours the child was in collapse; her eyes were sunken; the tongue was dry, and the abdomen was enormously distended. The stools were liquid and foul; the pulse rate was 160 per minute. The right leg was rapidly involved, and ulcerations with a putrid sanguinolent discharge appeared. Acute bronchitis now complicated the disease. Immediate amputation was advised, but the parents refused permission. The process proceeded to fatal termination on the third day.

AMESSE, Denver.

PROPHYLAXIS OF POLIOMYELITIS BY NASAL INSTILLATION OF ALUM. L. GENOESE, Méd. inf. **8**:197 (July) 1937.

This is a review of some North American literature on prophylaxis against poliomyelitis.

HIGGINS, Boston.

DIPHTHERIA. M. R. CAMPELLO, Arch. de pediat., Rio de Janeiro **9**:305 (July) 1937.

This is a résumé of the subject. The mortality in Brazil, on the average, is between 11 and 18 per cent.

SANFORD, Chicago.

PERTUSSIS IN BRAZIL. R. CARNEIRO and I. CARIAS DE OLIVERIA, J. de pediat., Rio de Janeiro **4**:217 (June) 1937.

The authors give in detail their results in 203 cases of whooping cough during the course of three epidemics. Their results with vaccine therapy were excellent, even when the vaccine was given during the disease. The vaccine used was made by the Institute Seroterapico Milanez. They are willing to admit that various epidemics in other countries may show differences in the results of vaccine therapy but in their case "our vaccine cures our whooping cough."

SANFORD, Chicago.

MALARIA TREATMENT OF POLIOMYELITIS. O. KAUDERS, Med. Klin. **33**:1502 (Nov. 5) 1937.

Kauders refers to his previous publications on the same subject in the same journal (*Med. Klin.* **32**:1729 [Dec. 18]; 1766 [Dec. 24] 1936). He used malaria treatment in a series of cases of poliomyelitis a considerable time after the onset and reports that in two cases (one with onset one-half year and the other with onset one year previously) marked improvement occurred. He emphasizes that improvement occurred in groups of muscles which were not completely atrophied. After discussing in detail the possible reasons for favorable results, partly on the

basis of an autopsy, he concludes that a lytic effect on infiltrations, an antiinflammatory action and a generally stimulating and favorable influence on the secretory processes of the spine-nerve-muscle system are factors. Physical therapy may enhance the good effects of malaria treatment. Kauders tried the malaria treatment soon after the acute stage of poliomyelitis in a few cases and observed favorable results in some and none in others. However, the period of observation was too short to permit definite conclusions. SIEMSEN, Chicago.

DICK TEST AMONG CHINESE. P. L. FAN, Chinese M. J. **51**:859 (June) 1937.

Fan reports Dick tests on four groups of persons—a group of children from orphanages, a group from rural schools, a group from hospitals and a group of both children and adults from other institutions—making a total of 3,825. Scarlet fever is rare in the southern provinces, less so in China as a whole.

Children in the preschool age gave positive reactions in from 60 to 80 per cent of the tests, indicating the greater danger at this age of life. Of the susceptible children 40 per cent were apparently children in the primary schools. Chinese girls show a higher percentage of positive reactions than boys. As age advances immunity increases. Placental immunity is at least one factor which usually protects young infants, there having been only 4.4 per cent positive reactions in the first half year of life. NEFF, Kansas City, Mo.

Acute Infectious Diseases

THE USE OF ANTIGONOCOCCAL SERUM, GONOCOCCAL VACCINE AND FILTRATE IN THE TREATMENT OF GONOCOCCAL INFECTIONS. CHESTER S. KEEFER and WESLEY W. SPINK, Am. J. Syph., Gonor. & Ven. Dis. **21**:241 (May) 1937.

A study was conducted along the lines indicated in the title. The authors' summary and conclusions were as follows:

"An experimental study of the immune reactions following the use of antigonococcal serum, gonococcal vaccine, and filtrate in patients with and without gonococcal infections disclosed the following:

"1. The bacteriolytic titer of the blood serum can be increased in vito and in vivo by the addition of antigonococcal serum.

"2. Recovery from gonococcal bacteremia is associated with an increase in the bacteriolytic titer of the serum. This may occur without specific treatment or it may be induced by the injection of serum.

"3. The injection of antigonococcal serum into the synovial cavity did not result in a sterilization of the synovial fluid.

"4. Repeated instillation of antigonococcal serum into the conjunctivae of a patient with gonorrheal ophthalmia did not sterilize the conjunctival sacs.

"5. Intravenous injection of vaccine in a patient with gonococcal infection increased the bactericidal power of the blood.

"6. Intradermal or subcutaneous injections of gonococcal vaccine were not followed by an increase in bacteriolytic titer but produced a positive complement fixation reaction.

"7. The intradermal injection of gonococcal filtrate did not increase the bacteriolytic titer of the blood in a normal individual." ROYSTER, University, Va.

THE CLINICAL USE OF SULPHANILAMIDE AND ITS DERIVATIVES IN THE TREATMENT OF INFECTIOUS DISEASES. PERRIN H. LONG and ELEANOR A. BLISS, Ann. Int. Med. **11**:575 (Oct.) 1937.

The experimental observations which led to the use of sulfanilamide are discussed.

The results of treatment in 4 cases of streptococcic meningitis are given in detail. In 2 of the 4 cases recovery followed without complications.

The toxic manifestations produced by sulfanilamide and its derivatives are carefully considered, especially those affecting the hemopoietic system.

The methods of administration of the drug are given. Attention is called to the importance of determining the amount of sulfanilamide in the blood four hours after the initial dose and at twenty-four hour intervals thereafter during the administration of the drug. The oral route is considered the safest and most effective for the administration of the drug.

It is suggested that sulfanilamide be used as a prophylactic agent in the prevention of streptococcic infections, especially in the face of epidemic outbreaks.

The careless and reckless use of sulfanilamide is unwarranted.

READING, Galveston, Texas.

BRUCELLA MELITENSIS MENINGITIS IN AN INFANT. ROBERT A. BLACK, Arch. Pediat. **54**:702 (Dec.) 1937.

A case in which a diagnosis of Brucella melitensis meningitis was confirmed at postmortem examination of a 4 month old infant is reported. No case has been previously reported in an infant.

ORR, Buffalo.

MODERN PROBLEMS IN THE CONTROL OF STREPTOCOCCIC DISEASES. JOHN H. BAILEY, Illinois M. J. **72**:301 (Oct.) 1937.

Evidence is gradually accumulating that there is a lack of specificity in the hemolytic streptococci and that any one of them may cause any of a number of conditions. Any one of a number of streptococcic diseases may be transmitted by a single person. Bailey believes that hemolytic streptococcic sore throat is the most important factor in the spread of streptococcic diseases and that control will come only when physicians recognize this fact and consider any hemolytic streptococcic sore throat as a source of danger to others—as a potential source of scarlet fever, erysipelas, puerperal sepsis or sore throat. He has little faith in active immunization against scarlet fever.

BARBOUR, Peoria, Ill.

METAPHEN INTRAVENOUSLY IN THE TREATMENT OF TULAREMIA. F. L. BARTHELME, Illinois M. J. **72**:317 (Oct.) 1937.

After a review of the literature on the treatment of tularemia, Barthelme reports his observations in 60 cases in which metaphen was used intravenously. He found the treatment to have no harmful results. The duration of the fever was eleven days. The average duration of adenopathy was not over twenty-four days. The disease lasted an average of thirty-two days. There was no case in which the glands required incision.

BARBOUR, Peoria, Ill.

TREATMENT OF ACUTE RHEUMATIC POLYARTHRITIS WITH CONCENTRATED ANTISCARLATINAL SERUM. JOHN EASON and GURTH CARPENTER, Quart. J. Med. **6**:93 (April) 1937.

Because of the high incidence of relapse and of cardiac sequelae in persons with rheumatic polyarthritis who are treated with salicylates, the authors tried the administration of concentrated antiscarlatinal serum. In spite of the admitted difficulties involved in evaluating serum therapy in this type of disease, they concluded that it was an effective form of therapy, worthy of extended trial.

As compared with salicylate therapy, serum treatment had certain advantages: (1) In certain cases a condition resistant to the salicylates was effectively treated with serum; (2) the incidence of relapse was lower with serum, and (3) the length of stay in the hospital and the duration and nature of the convalescence compared favorably with the following use of the salicylates.

Untoward results of serum therapy were: (1) local reactions as a result of the intramuscular injection of 30 cc. of the material, (2) immediate exacerbation

of temperature and (3) 75 per cent incidence of serum disease. One serious reaction, an alarming collapse with dyspnea, cyanosis and tachycardia observed on the eighth day after administration of serum, was ascribed to the serum.

The authors conclude that it is safe to give serum to very ill patients, even those suffering from grave carditis.

The reviewer does not think that distinct advantages of this form of therapy have been proved by the material presented. It is surprising, however, that the hyperallergic subjects treated tolerated the administration of serum as well as they apparently did.

BRADFORD, Rochester, N. Y.

THE SEARCH FOR LEISHMAN'S PARASITE BY MEANS OF DERMAL SCARIFICATIONS. F. MARTILLOTTI, Pediatria **45**:213 (March) 1937.

According to the author, many experimenters have tried to prove the presence of Leishman's parasite in preparations from dermal scarifications in babies affected internally with leishmaniasis.

He states, however, after long and tedious work, that such a search is unreliable and its results difficult to interpret. The best materials to examine for the parasite are still the splenic pulp and the marrow.

PALMIERI, Brooklyn.

DOSAGE IN THE TREATMENT OF MALARIA OF CHILDHOOD. F. RONNEFELDT, Klin. Wchnschr. **12**:986 (June 24) 1933.

This report covers treatment with atabrine (a derivative of acridine) in 37 West African children suffering from malaria. The standard dosage starts with 0.1 Gm. for children up to 5, 0.2 Gm. for children from 5 to 10 and 0.3 Gm. for children over 10 (adult dose). Ronnefeldt states that since this drug appears to have a direct effect on the parasites, the dose is dependent on the number of parasites rather than on the body weight, and therefore a relatively higher dose is required in children. Individual variations are encountered, but rickets in particular appears to have a bearing on the dose required to effect a cure.

SILVERMAN, Syracuse, N. Y.

Chronic Infectious Diseases

CERTAIN ASPECTS OF CHILDHOOD TUBERCULOSIS. R. M. TYSON, J. A. M. A. **109**: 753 (Sept. 4) 1937.

At present the common idea is that most tuberculous infections are air borne and gain entrance into the human body by way of the pulmonary structures. The method of primary infection consists of penetration of the pulmonary structures, followed by lymphangitis along the pathways and lymph adenitis. Dissolution of the lipoid capsule of the tubercle bacillus liberates tuberculoprotein, which sensitizes the tissues of the patient and produces recognizable clinical symptoms. At the end of the primary period, lasting from three to six weeks, a positive reaction to the tuberculin test may be obtained. Often changes are not demonstrable clinically or roentgenologically at this time. In the second, postprimary clinical stage, there is usually definite clinical, pathologic and roentgen evidence of reinfection and expansion. Reinfections are probably the result of rupture of a lymph node or a tubercle into a new lymph node, a bronchus, the blood or the lymph stream. The third, active, stage of the disease occurs most often in adult life. The higher incidence of deaths from tuberculosis in infants than in older children is probably not so much due to lack of resistance as to the child's smaller opportunity for evading repeated and massive doses of living bacilli. However, poor hygiene plays an important part. Early diagnostic signs are: stationary or diminishing weight without any obvious cause; appearance of indefinite irritability, fretfulness, fatigue and lack of appetite, and elevation of temperature. Later signs, the result of

reinfection and increasing toxemia, are: lusterless eyes, heavy long eyelashes, pouty lips, dry skin and hair and hypertrichosis. The Mantoux test is extremely valuable, and serial roentgen studies are of more value than single studies. The gastric contents and even the stools may reveal organisms. Prevention of tuberculosis in children is most successfully accomplished by keeping them from coming in contact with patients with open disease. Isolation of tuberculous patients is necessary before this can be accomplished.

BONAR, Salt Lake City.

CONGENITAL SYPHILIS IN SMALL TOWNS AND RURAL DISTRICTS. CHRISTOPHER ROLLESTON, Brit. J. Child. Dis. **34**:165 (July-Sept.) 1937.

During twelve years Rolleston collected 50 cases of congenital syphilis from a population of 70,000. The oldest patient in the series was 45 and the youngest 10 weeks old. In 29 of the cases 1 or both of the parents had a positive Wassermann reaction.

In 2 cases no definite signs or symptoms were found. Ocular lesions were present in 31 cases, some abnormality of the permanent dentition in 21 and impairment of hearing in only 3.

Rolleston stressed the importance of early treatment. Prolonged treatment in cases of interstitial keratitis with arsenic and bismuth preparations gives excellent results, but the results in cases of choroidoretinitis and of cerebrospinal syphilis are poor.

LANGMANN, New York.

PULMONARY TUBERCULOSIS IN CHILDREN. AGNES R. MACGREGOR and W. A. ALEXANDER, Edinburgh M. J. **44**:561 (Sept.) 1937.

This leading article comes from the Royal Hospital for Sick Children, Edinburgh University, and the Research Laboratory at the College of Physicians.

In vast numbers of cases primary pulmonary lesions never declare themselves as tuberculosis of the lungs, so that the truth of the dominant role played by the lungs as a point of entry for tuberculosis is obscured. Autopsies in 333 cases of tuberculosis showed that the disease originated in the lungs in 60 per cent. Of 200 patients whose primary involvement was in the chest, 80 per cent died of meningitis.

The report covers the origin and development of those tuberculous processes in the lungs which come from a first infection. The gross and the minute characters of the lymph glands are discussed in relation to the primary pulmonary focus. The primary pulmonary focus results from direct inhalation of tubercle bacilli from an external source.

Roentgenograms taken during life showed it often to be impossible to detect in the film the pulmonary focus discovered at autopsy, except in cases in which the focus is larger than usual. Even the enlarged caseous glands were hard to visualize.

Progressive and permanent extensions usually represent the change of the primary pulmonary focus into a larger lesion or the extension of an infection of the root of a gland outward into the lungs. There may occur areas of caseous pneumonia and areas of proliferative infiltration. Some extensive localized lesions in tuberculous children are not necessarily fatal but may eventually disappear, leaving no trace or only slight scars visible in the film. The author discusses the explanations which have been offered for the disappearance of these lesions, namely, collapse, a nontuberculous pneumonia or a true tuberculous process.

Widespread dissemination may come from the infection within the lungs if not interrupted by fatal metastasis, such as meningitis. There are disseminations from blood-spread infections which produce acute, subacute or chronic miliary lesions. Proliferative foci are distributed in the same haphazard way as acute miliary lesions, while exudative foci produce a notable form of tuberculosis in which the lungs are voluminous, heavy and almost deprived of air. The lesions are typical exudative tubercles.

The widespread dissemination of lesions may be by way either of the bronchi or of the blood stream.

The paper is illustrated with photographs of the primary pulmonary complex, cavities, exudative miliary lesions, large sections of lung and photomicrographs.

NEFF, Kansas City, Mo.

OBSERVATIONS ON PULMONARY TUBERCULOSIS IN CHILDREN. JOHN HOUSTON, Edinburgh M. J. **44**:653 (Oct.) 1937.

In 64 per cent of 87 consecutive cases it was possible to obtain sputum for examination. In 6 of the cases bacilli were recovered from the gastric washings; in 7 others there were nonpulmonary sources of proof, while in the 8 remaining cases the postmortem examination confirmed the diagnosis of tuberculosis.

As to attempts at culture, it was found that nearly all strains of the bacilli grew well in artificial mediums, but implantation in rabbits showed a low degree of pathogenicity or virulence. The infection belonged to the human strain in 81 instances.

The author cites the autopsies of 6 children with pulmonary disease who had either bovine or mixed bovine and human infection. It was not possible to find any clinical or pathologic difference between these types and the human type of infection alone.

Infection by contact with patients with open pulmonary tuberculosis was known to have occurred in 23 of the cases of infection of the human type.

NEFF, Kansas City, Mo.

THE TRYPTOPHANE REACTION AS AN AID TO THE EARLY DIAGNOSIS OF MENINGEAL TUBERCULOSIS. HENRY BAXTER, Edinburgh M. J. **44**:663 (Oct.) 1937.

In many instances of meningeal tuberculosis the causative bacillus cannot be demonstrated in the spinal fluid during life. Physicians should welcome as an aid to its early demonstration such a simple indicator as the tryptophan reaction. It is best observed in a clear spinal fluid early in the disease and consists of a characteristic delicate violet ring in the test tube when the reagents mixed with spinal fluid are layered with solution of sodium nitrite.

NEFF, Kansas City, Mo.

THE EARLY DIAGNOSIS AND TREATMENT OF TUBERCULOSIS OF BONES AND JOINTS IN CHILDREN. PHILIP WILES, Practitioner **139**:540 (Nov.) 1937.

"The pathological changes in tuberculosis in bones and joints are similar to those occurring at other sites. Bones and joints, however, are never the seat of a primary tuberculous infection; spread always occurs from some other focus in the body by the blood stream or perhaps the lymphatic system. Tubercle bacilli travel by one or other of these routes and settle in the neighbourhood of a joint, either in the synovial membrane or in the adjoining bone. Argument as to which is usually infected first is of little practical importance, since spread from one to the other generally occurs sooner or later. Whether the disease is primarily synovial or bony, the earliest changes are usually seen near the circulus vasculosus of the joint. Metaphysial infection sometimes occurs, as is common in acute pyogenic osteomyelitis, but this is exceptional. . . .

"The great majority of cases in children occur in the spine and hips; the knee and foot are the next most common sites. . . .

"The earliest signs of disease of a joint are *pain* and *limitation of movement.* They are not diagnostic of tuberculous disease, but every child having these two signs in the hip or back, without other known cause, should be regarded as having tuberculosis until the contrary has been proved. . . .

"*Pain* is not necessarily localized to the affected joint, but may be referred to distant points. . . .

"*Limitation of movement* is due to spasm of the muscles controlling the affected joint, and is the most important sign of disease of a joint. . . .

"Pain and limitation of movement merely indicate some disorder of a joint, the nature of which it is essential to determine. . . .

"Tuberculosis of bone and joint is a local manifestation of a general disease. The disease has not originated locally, but has spread from some focus elsewhere in the body. . . .

"There has been much controversy as to the right moment for surgical interference with a tuberculous joint. Practice has fluctuated from early excision of the joint to complete denial of the value of surgery. The modern tendency is a mean between these extremes."

GELSTON, San Francisco.

SYPHILITIC OSTEOCHONDRITIS WITH PSEUDOPARALYSIS OF PARROT. JESUS ALFREDO FIGUERAS, Arch. de méd. inf. **6**:286 (Sept.) 1937.

Every case of osteochondritis in an infant in which roentgenograms show a picture pathognomonic of syphilis should be considered as an instance of congenital syphilis, even if serologic tests are negative. The paralytic syndrome of Parrot is not common.

SANFORD, Chicago.

TUBERCULOUS PERITONITIS OF ASCITIC FORM IN CHILD SEVENTEEN MONTHS OLD. PIERRE BARBÉ, Bull. Soc. de pédiat. de Paris **34**:784 (Dec.) 1936.

A boy 17 months old had had enlargement of the scrotum and the abdomen for three months. A tuberculin test gave positive results. Yellowish fluid was removed from the abdomen. The ascites disappeared gradually over a period of four months, and the hydrocele took a few months more to be absorbed, after which a slight induration remained along the right spermatic cord. The child's general condition remained good throughout the course of the disease, and he had no fever at any time. The condition is rare in so young a patient.

BENJAMIN, Montreal, Canada.

TUBERCULOUS TUMOR OF THE MEDIASTINUM: CEREBRAL METASTASIS. H. GRENET, R. LEVEUF and P. ISAAC-GEORGES, Bull. Soc. de pédiat. de Paris **35**:158 (March) 1937.

A boy 4 years old had signs and symptoms of a mediastinal tumor and a cerebral lesion. Necropsy revealed the true nature of the lesions, which were tuberculous. The roentgenologic shadow produced by the mass in the chest was homogeneous and had regular edges, and was apparently due to mediastinitis as well as to enlargement of the glands. Roentgen therapy had produced marked shrinkage of the tumor without any improvement in the general condition of the child. Contrary to some experience with roentgen therapy applied exteriorly to tuberculous glands, suppuration did not take place and there was considerable fibrosis of the glands.

BENJAMIN, Montreal, Canada.

FATAL ACCIDENT OF AN INFANT WITH HEREDITARY SYPHILIS TREATED BY MERCURIAL INUNCTIONS. J. FLEURY and J. AUPERIN, Bull. Soc. de pédiat. de Paris **35**:182 (March) 1937.

A 15 day old boy had congenital syphilis, with marked involvement of the liver, spleen and one testicle. He was given mercurial inunctions, and after one week of this treatment the liver and spleen diminished considerably in size, but edema, oliguria and convulsions developed. He had marked retention of urea and slight albuminuria without casts. Terminally he showed deep jaundice and hemorrhages from the intestinal tract. Although the prognosis of infants with severe syphilitic visceral involvement is poor and there were none of the usual accompaniments of mercurial poisoning in this case, it is felt that when the liver and spleen show such marked reaction to treatment medication should be temporarily stopped. Possibly small doses of mercury by mouth might be safer in such a case.

BENJAMIN, Montreal, Canada.

Diseases of Blood, Heart and Blood Vessels and Spleen

SEASONAL VARIATIONS IN THE NUMBER OF PLATELETS IN ARTERIAL, VENOUS AND CUTANEOUS BLOOD OF MAN. L. M. TOCANTINS, Am. J. Physiol. **119**:439 (July) 1937.

Platelet counts were made simultaneously on arterial, venous and cutaneous blood from the same extremity of healthy young adults during different seasons of the year. It was found that the number of platelets in arterial and in venous blood from the upper extremity in man is significantly higher in winter than in spring; there is no significant difference between counts on cutaneous blood in the two seasons. In the winter, the number of platelets is significantly higher in arterial blood than in venous blood; it is also significantly higher in venous than in cutaneous blood. In the spring there is no statistically significant difference between the means of platelet counts on blood from the three sources. There is no statistically significant difference between the erythrocyte counts in the two seasons.

During the spring there is a greater frequency of attacks of purpura and thrombopenia than at other times of the year. Tocantins points out that perhaps when the decrease in the number of platelets in the spring occurs in the blood of persons who usually have counts lower than normal the result is marked thrombopenia.

NOURSE, Cleveland.

ACUTE HEMOLYTIC ANEMIA DURING TREATMENT WITH SULFANILAMIDE. S. E. KOHN, J. A. M. A. **109**:1005 (Sept. 25) 1937.

The author reports a case of anemia accompanied with acute hemolysis and hemoglobinuria in a girl of 1 year who was given sulfanilamide for the treatment of an acute infection of the upper part of the respiratory tract due to the hemolytic streptococcus. The child recovered.

BONAR, Salt Lake City.

PURPURA HAEMORRHAGICA. M. M. WINTROBE, E. M. HANRAHAN JR. and C. B. THOMAS, J. A. M. A. **109**:1170 (Oct. 9) 1937.

The varied course of purpura haemorrhagica, with spontaneous remissions, relapses and recurrence years later, makes it necessary to study patients many years after treatment. Sixty-two cases of purpura haemorrhagica were observed, in 64 per cent of which the duration had been more than three years. In 19 the spleen had been removed. With medical care recovery is the rule, but recurrence is common, especially in female patients. The authors believe there is no adequate evidence for considering splenectomy a specific treatment for purpura haemorrhagica. Recurrence may follow operation; nevertheless operation is the most effective of the therapeutic methods so far proposed.

BONAR, Salt Lake City.

THE HAEMORRHAGIC STATES. L. J. WITTS, Brit. M. J. **2**:689 (Oct. 9) 1937.

The author opens his discussion by stating the difficulties of schematic presentation in a discussion of anemia. He feels that the hemorrhagic states are dealt with not according to a single cell system but with the complex and interlocking mechanism of hemostasis, in which the plasma, the platelets, the endothelial lining of the vessels and the connective tissue all participate. He distinguishes hemophilia and related conditions, in which the blood does not clot normally, from purpura and hemogenia, in which the blood clots with normal speed but the bleeding time is prolonged.

There follows the classification of Davidson according to idiopathic or symptomatic etiology and according to thrombopenic or nonthrombopenic morphology. Each type is then discussed, and possible or speculative factors are considered.

The study is concluded with the following summary:

"1. Hereditary haemorrhagic states show considerable diversity in symptoms and mode of inheritance.

"2. The local application of coagulant venoms is the only considerable advance of recent years in the treatment of the haemorrhagic diseases. The value of liver, oestrin, moccasin venom, and the Sheffield extract of egg albumen has not been confirmed.

"3. Splenectomy remains the most successful treatment for idiopathic thrombocytopenic purpura, but the frequency of relapses suggests that the operation is a temporary stimulus to platelet production rather than a specific cure for the disease.

"4. Vitamin C is of value only in scurvy, whether overt or latent. It is not a general or non-specific remedy for haemorrhagic states. Nevertheless the isolation of ascorbic acid is of especial importance as it marks the impact of biochemistry on the haemorrhagic states and a probable improvement in the technique of investigation."

ROYSTER, University, Va.

THE CLINICAL PATHOLOGY OF HAEMORRHAGIC STATES. S. C. DYKE, Brit. M. J. **2**:692 (Oct. 9) 1937.

The author discusses the pathologic picture of hemorrhagic states under the following headings: bleeding time, blood picture, blood platelets, scurvy, coagulation time, postoperative hemorrhage and nephritis.

He concludes with the following paragraph:

"The haemorrhagic state may present itself in the course of many acute infections and septic conditions. In these cases its establishment appears to be due to damage sustained by the capillary walls as a result of the infection. The differentiation of cases having an infective basis from those mentioned above seldom presents any great difficulty: their clinical pathology is that of the causative infection.

ROYSTER, University, Va.

A STABLE FERROUS SULPHATE MIXTURE FOR THE TREATMENT OF NUTRITIONAL ANAEMIA IN YOUNG CHILDREN. HELEN M. M. MACKAY and LYDIA E. JACOB, Lancet **2**:570 (Sept. 4) 1937.

Treatment of 26 babies with iron deficiency anemia with doses of 4½ or 9 grains (0.29 or 0.58 Gm.) of ferrous sulfate daily produced an average daily rise in hemoglobin level of almost 1 per cent during the first three to five weeks of treatment.

The prescription used was: ferrous sulfate, 1½ grains (0.09 Gm.); dilute hypophosphorous acid, ¼ minim (0.015 cc.); dextrose, 15 grains (1 Gm.), and chloroform water to make 1 fluidrachm (3.7 cc.).

The dilute hypophosphorous acid was added to the dextrose to prevent oxidation. This mixture will keep for over two months.

LANGMANN, New York.

HYPOPLASIA OF AURICLE WITH TRICUSPID STRAIGHTENING AND PULMONARY CONSTRICTION. RENE MONTERO and ARGELIO GARCIA, Arch. de méd. inf. **6**:268 (Sept.) 1937.

The authors report a case in which cyanosis, dyspnea, ascites and edema of the face were present. The roentgenogram showed a trilocular heart, and the electrocardiogram showed an accentuated P wave. The autopsy showed hypoplasia of the

auricle, tricuspid straightening of postnatal infectious origin and narrowing of the pulmonary artery. The ductus arteriosus was completely obliterated. Photographs of the condition are shown.

SANFORD, Chicago.

DIAGNOSIS OF PERICARDITIS IN INFANTS. J. WOLFF, Kinderärztl. Praxis **9**:59 (Feb.) 1938.

Wolff emphasizes the fact that even without a friction rub and roentgen evidence a diagnosis of pericarditis can be made for an infant, because he has observed that both heart sounds suddenly become diminished in intensity when pericarditis develops. In myocarditis, only the first heart sound is similarly indistinct. The diagnosis of pericarditis for an infant is permitted on the basis of observation of heart failure without murmurs, even without a friction rub, which often persists for a short time only, when both heart sounds become faint and subdued.

HEYMANN, Cleveland.

A CASE OF SCHÜLLER-CHRISTIAN'S SYNDROME. S. SAITŌ, Orient. J. Dis. Infants **21**:287 (March) 1937.

The author reports a case of Schüller-Christian's disease in a girl 7 years and 8 months old, in which the significant manifestations were (*1*) polyuria, (*2*) lesions of xanthoma originating in the left eyelid and gradually extending over the entire face and (*3*) slight widening of the sella turcica. The roentgenograms of the skull, however, revealed no bony defects. The treatment consisted of daily injections of 0.1 cc. of solution of posterior pituitary subcutaneously and appeared to have favorable effects on the symptoms. No record of autopsy is given.

KATO, Chicago.

Diseases of Nose, Throat and Ear

INCREASED ACOUSTIC SENSITIVITY IN DOGS FOLLOWING ROENTGEN-RADIATION OF THE HYPOPHYSIS. W. J. BROGDEN and E. CULLER, Am. J. Physiol. **119**:13 (May) 1937.

Increased acuity of hearing was produced in dogs by roentgen irradiation of the head. This was shown to be due to the effect on the hypophysis from the lowering of the blood sugar. A diabetic subject and also a normal dog showed increased acuity when the blood sugar was lowered with insulin and reduced sensitivity when the blood sugar was raised.

NOURSE, Cleveland.

PRENATAL AND POSTNATAL DEVELOPMENT AND FORM OF CRYPTS OF THE HUMAN PALATINE TONSIL. W. L. MINEAR, L. B. AREY and J. T. MILTON, Arch. Otolaryng. **25**:487 (May) 1937.

The authors present the life history of the crypt system in the human palatine tonsil from a study of serial sections and wax reconstructions of the tonsil at significant stages from the first budding of prenatal life to the atrophic tonsil of old age.

The crypts of the human palatine tonsil appear first during the third fetal month as solid ingrowths from the epithelial wall of the tonsillar fossa. These epithelial processes grow, branch and canalize. The first phase in the development of the crypt system is characterized by a peculiarity of growth owing to which many of the epithelial ingrowths form epithelial vesicles (cystic crypt), the majority of which disappear shortly after birth. Some of them may persist in adult life. The second phase is characterized by the appearance of new first order crypts and by further growth of the first and second order crypts which

escape destruction during the first phase. The full number of crypts is obtained sometime during early childhood. The crypts later elongate and enlarge by interstitial growth to form a definite crypt system. The number of the first order crypts remains relatively constant until the onset of tonsillar senescence. The curved or flat platelike type of cyst is predominant. Many of the large first and second order crypts have constricted necks. The size and complexity of crypts are greater in the superior half of the tonsils than in the lower half.

The final phase is marked by progressive atrophy and degeneration, reminiscent of the late prenatal and early postnatal period. The inferior half of the tonsil is the first to degenerate. Atrophy of lymphoid tissue and compensatory formation of fibrous tissue accompany the degeneration of the crypt system. The approximate area of epithelial lining of the adult crypt system of one tonsil was calculated to be 46 square inches (295 square centimeters), whereas the exposed surface area of the entire pharynx was only 7 square inches (45 square centimeters). Any tendency to empty the tonsillar crypts through natural or artificial means must necessarily be highly inefficient owing to anatomic constrictions and the tendency of the contents of a complex convergent system to become impacted at the bottle neck region of the main crypt. Such plugging is further enhanced by the fact that the main drainage channel is often smaller than its tributaries.

GREENWOOD, Chicago.

PARANASAL SINUSITIS. SIDNEY SAMUEL DUSHAN, Arch. Pediat. **54**:643 (Nov.) 1937.

Sinusitis may be classified as extrinsic, intrinsic or of physical or chemical origin. Either of the first two types may be acute or chronic. The extrinsic type is due to foods or excitants; the intrinsic, to bacterial infection. The last type is due either to heat and cold or to chemicals, and represents only a small proportion of cases of sinal disease.

ORR, Buffalo.

IRRADIATION AS TREATMENT OF NONSPECIFIC COUGH IN CHILDREN. IRA I. KAPLAN, Arch. Pediat. **54**:699 (Dec.) 1937.

Roentgen irradiation has a definite therapeutic value in the treatment of persistent cough that fails to respond to other measures.

ORR, Buffalo.

OTITIS MEDIA IN INFANCY. JOSEPH R. DOLCE, Arch. Pediat. **54**:734 (Dec.) 1937.

Three cases in which otitis media was the source of fever in a newborn infant are reported.

ORR, Buffalo.

THE PROPER CRITERIA FOR LIP READING RECOMMENDATION: MEDICAL AND EDUCATIONAL CONSIDERATIONS. MOSES L. BREITSTEIN and OLIVE WHILDIN, South. M. J. **30**:924 (Sept.) 1937.

After examinations and hearing tests have established the diagnosis of permanent or progressive deafness, the problem of lip reading must be immediately settled. Several questions must be answered before a decision can be reached: 1. Is the deafness monaural or binaural? 2. Does the loss of hearing lie in the range of speech? 3. Is the patient working up to the level of his ability in school? 4. Is he happily adjusted in his class, socially and physically? 5. Is his behavior natural and acceptable? 6. Is there any indication of deafness in his speech? The answers to these questions will determine the child's need for lip reading.

Follow-up and retesting in any case in which deafness is suspected is of greatest importance.

In cases in which the destructive process of purulent otitis media has not advanced too far, treatment, either local or operative, which has improved the local aural condition has likewise improved the hearing.

SCHLUTZ, Chicago.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

Relation of the Size of the Meal to the Emptying Time of the Human Stomach. E. J. Van Liere, C. K. Sleeth and D. Northup, Am. J. Physiol. **119**:48 (July) 1937.

The emptying time of the stomach with a standard test meal of farina mush was determined fluoroscopically in 6 healthy young adults. With a meal twice the size of the standard meal the emptying time was prolonged 16.83 per cent in 5 of the 6 subjects, and with a meal three times the size of the standard meal, 38.33 per cent in 5 of the 6 subjects. One subject showed no change. The authors suggest that increased amount of food causes distention of the stomach, which stimulates it to more effective contractions. This paper lends experimental evidence to the well recognized fact that the onset of contractions due to hunger does not in the majority of people appear as soon after a large meal as after a small one.

Nourse, Cleveland.

The Injection Treatment of Reducible Inguinal Hernia in Children. Franklin I. Harris and Alfred S. White, Arch. Pediat. **54**:665 (Nov.) 1937.

The prime requisite for the injection treatment of inguinal hernia in children is that the hernia be completely reducible and the reduction maintainable at all times during the course of treatment by a properly fitting truss. The type of truss most suited for children is the semirigid one with posterior counterpressure and a beveled sponge-rubber pad. Occasionally a rigid truss with bilateral posterior counterpressure is necessary. The truss must be worn day and night during the course of injection and for eight weeks thereafter. Before treatment is begun every difficulty involved in the fitting and wearing of the truss must be adjusted. This may take from one to three weeks. Once the treatment is begun, the truss must never be removed except by the physician for treatment.

Injections are given twice weekly in the region of the internal ring until that area is filled with a plastic exudate. This requires from three to five injections. Further injections are given along the inguinal canal toward the external ring. The number of injections in any given case depends on two factors: the size of the hernia and the seroplastic reaction of the subject. A minimum of from five to eight should be given, and the number will rarely exceed ten. After the last injection the patient must continue to wear the truss day and night for four weeks to allow the newly formed fibroblastic tissue to grow strong. Infants should wear a truss for an additional four weeks. The solution used is the sodium salt of the fatty acid of oil of psyllium. The recommended dose is: for patients under 1 year of age, 0.5 cc.; for those from 1 to 4 years of age, 0.75 cc.; for those from 4 to 8 years of age, 1 cc., and for those from 8 to 14 years of age 1.25 cc., at each injection.

Fifteen cases of indirect reducible inguinal hernia were treated by the injection method. In 12 the lesion has remained closed for follow-up periods of from six to thirty months after complete removal of the truss; in 2 the condition has recurred, and in 1 treatment was discontinued.

Orr, Buffalo.

Nutritional Edema in Children. J. I. Waring, Arch. Pediat. **54**:674 (Nov.) 1937.

Two cases are reported.

Orr, Buffalo.

Congenital Stricture of the Esophagus. Archibald D. Smith, Arch. Pediat. **54**:678 (Nov.) 1937.

A case is reported.

Orr, Buffalo.

SURGICAL MANAGEMENT OF ACUTE APPENDICITIS AND ITS COMPLICATIONS IN CHILDREN. EDWIN M. MILLER and EDGAR C. TURNER, Illinois M. J. **72**:222 (Sept.) 1937.

The authors present the results of a three year study of acute appendicitis and its complications in 613 cases in the Children's Ward of the Cook County Hospital. From these observations they arrive at the following conclusions:

"1. Immediate appendectomy is indicated in all cases of acute appendicitis before perforation, unless the infection is very clearly subsiding. 2. When the clinical evidence shows that the appendix has ruptured and the infection is definitely localized as evidenced by a palpable inflammatory mass, a conservative course should be followed in the vast majority of cases. Only a very few will demand surgical drainage. 3. In all cases in which a spreading peritonitis is present without evidence of localization, it is a wise plan to remove the source of the infection, institute proper surgical drainage, and use whatever means available to diminish the amount of distention of the bowel with gas."

BARBOUR, Peoria, Ill.

DIAGNOSIS OF ACUTE APPENDICITIS IN CHILDREN. H. W. ELGHAMMER, Illinois M. J. **72**:232 (Sept.) 1937.

Elghammer reviews the symptoms, signs and differential diagnosis of acute appendicitis in children. He points out that the symptoms and signs in the first five years of life and in later periods differ distinctly. The difficulty of diagnosis in children is emphasized. For any young child with restlessness, abdominal pain, vomiting and low grade fever a diagnosis of appendicitis should be considered. Observation of general postural characteristics and certain methods of examination peculiar to children are of importance in the diagnosis. In early diagnosis and the avoidance of cathartics lies the hope of decreasing the mortality from appendicitis in children.

BARBOUR, Peoria, Ill.

CHILDHOOD APPENDICITIS. THERESA O. SNAITH, West Virginia M. J. **33**:451 (Oct.) 1937.

This paper presents a plea for early diagnosis and treatment of appendicitis in children. The burden of responsibility for diagnosis and outcome rests on the medical attendant.

The mortality for appendicitis has not decreased since the day of Murphy. Two thirds of the deaths occur in patients under 12 years and over 40, although only one third of all the patients are in those age groups. The death rate is about the same for children and adults in cases in which the appendix has not ruptured and in cases of abscess but is about doubled for children in cases of rupture without localization of peritonitis. This indicates a lower peritoneal resistance in children and emphasizes the importance of early diagnosis.

A number of cases in the first three months of life have been reported.

The exact cause of appendicitis is still in doubt. Various etiologic factors are discussed.

The symptoms are similar in adults and in children but are often shrouded in children by other gastrointestinal conditions. Pain is the earliest symptom, and in its absence a diagnosis of appendicitis is doubtful. Location of the pain is variable. Nausea and vomiting are the symptoms of next importance, occurring in about 80 per cent of cases. Localized tenderness and rigidity are usually present, and their absence probably explains failure in diagnosis in some cases.

A disproportionately rapid pulse is a reliable sign. In the young child diarrhea immediately precedes the attack, in contrast to the picture in the adult. Acetonuria and flexed thighs are indications of importance. High temperature and leukocytosis suggest complications. Referred pain from pneumonia or from diaphragmatic

pleurisy frequently causes difficulty in differentiation. Pyelitis, retroperitoneal adenitis, psoas abscess, intussusception, ureteral calculi, cyclic vomiting and allergy must be eliminated in the diagnosis.

The author gives this quotation from the noted English surgeon Bastianelli: "When physicians are discussing whether the case is appendicitis or not, it is. When they are inclined to admit the possibility of appendicitis without being perfectly sure of it, it not only is, but is about to perforate. When the diagnosis is sure, there is already perforation with more or less circumscribed peritonitis."

SHAWKEY, Charleston, W. Va.

INTESTINAL OCCLUSION IN THE NEWBORN. M. HUERGO and F. SALAS PANICELLO, Arch. de méd. inf. **6**:300 (Sept.) 1937.

Five instances of intestinal occlusion in the newborn are reported, the condition being due in 1 to an imperforate diaphragm in the third portion of the duodenum, in 2 to a cordlike atresia of the last portion of the ileum, in 1 to complete interruption of the ileum and in 1 to chronic mesenteritis. The initial symptom was vomiting beginning twelve hours after birth. In all cases meconium and cornified epithelial cells were absent. Early surgical intervention did not prove successful.

SANFORD, Chicago.

TREATMENT OF INTOXICATION IN INFANTS BY CONTINUOUS INTRAVENOUS INSTILLATION (METHOD OF KARELITZ AND SCHICK). ROBERT DEBRÉ, JULIEN MARIE, M. L. JAMMET and P. FONT-RÉAULX, Bull. Soc. de pédiat. de Paris **34**:764 (Dec.) 1936.

Infants with marked acute dehydration were given from 400 to 800 cc. of dextrose and saline solution in twenty-four hours by continuous intravenous administration. The treatment was usually continued for three days. During the first two days nothing was permitted to be taken by mouth; on the third day feeding was started, and it was gradually increased. Some spectacular results were obtained, but some infants died, even after dehydration had been corrected, on account of severe toxemia due to persisting infection. Medicaments such as epinephrine and insulin were administered intravenously by adding them to the solution used.

BENJAMIN, Montreal, Canada.

DUODENAL STENOSIS IN INFANT ONE MONTH OLD. ROBERT DEBRÉ, JULIEN MARIE, LÉONET and S. BIDOU, Bull. Soc. de pédiat. de Paris **34**:774 (Dec.) 1936.

A boy 1 month old began projectile vomiting when 8 days old. He had intermittent distention of the upper part of the abdomen, where visible peristalsis was observed, and some constipation was present. Roentgen examination revealed duodenal stenosis. Surgical intervention was unsuccessful. At necropsy the small and the large bowel were observed to be free from the mesentery, and the duodenum was constricted under the root of the mesentery.

BENJAMIN, Montreal, Canada.

LYMPHOCYTOMA OF DUODENUM IN A CHILD TWELVE YEARS OLD: OBSTRUCTION OF PRINCIPAL BILIARY ROUTE. CASSOUTE, SALMON, MONTUS and J. VAGUE, Bull. Soc. de pédiat. de Paris **34**:780 (Dec.) 1936.

A boy 12 years old had obstructive jaundice, which cleared temporarily and then became more marked over a period of two months. There were epigastric pain, which came on about half an hour after meals, anorexia and some loss of weight. A hard tumor the size of a fist was palpable in the epigastric region to the right of the midline. Roentgen examination showed this to be above the mesocolon, compressing the transverse colon and apparently attached to the liver. A tube

inserted in the stomach could not be passed beyond the pylorus, and hemorrhagic fluid was withdrawn from the stomach. At operation the tumor was found to be in the posterior part of the duodenum adherent to the prevertebral tissues. A biopsy was done and cholecystogastrostomy performed. The boy died. At necropsy the tumor was found to occupy the second part of the duodenum, where the latter was of twice normal size. It invaded the pancreas and compressed the bile duct. There were a number of enlarged regional lymph glands. The diagnosis was lymphocytoma.

BENJAMIN, Montreal, Canada.

THE PATHOLOGIC BACKGROUND OF CYCLIC VOMITING WITH ACETONURIA. A. G. ALARCON, Rev. mex. de puericultura **1**:121 (Feb.-April) 1937.

In cyclic vomiting the hyperexcitability of the sensitive motor system is probably determined by intoxication from a neurotrophic vagomimetic factor created in the organism by a perversion of fat metabolism. This supposition is based on the following observations: 1. There is a relation between the frequency of the phenomenon and the presence of fat in the food. 2. Fasting is a decisive factor in the correction of the syndrome. 3. It is possible to prevent the condition by means of the diet. 4. There is a frequent coincidence between the presence of the symptoms and improper fat metabolism producing acetonemia and acetonuria.

HERRON, Monroe, La.

CARCINOMA OF THE CECUM IN A FIFTEEN YEAR OLD GIRL. F. SETTERGREN, Nord. med. tidskr. **13**:593 (April 10) 1937.

At an operation for acute appendicitis, a walnut-sized soft tumor of the cecum was found and extirpated. Histologic examination showed adenocarcinoma. A second operation was performed and the cecum and the ascendant colon resected. Half a year later the girl was in an excellent state of health and had had no abdominal symptoms.

WALLGREN, Göteborg, Sweden.

Nervous Diseases

ASTROCYTOMA. B. J. ALPERS and S. N. ROWE, Am. J. Cancer **30**:1, 1937.

The practical advantages of a clinicopathologic classification of a group of varying tumors of the brain are obvious. With the accumulation of pathologic data and the more careful delineation of clinical pictures, more accurate preoperative diagnoses may be achieved, and the operative attack on the lesion may be planned and executed more intelligently. After histologic examination of the tumor, either through immediate biopsy or through postoperative examination, such vital questions as the radicalism of the removal, the advisability of irradiation, the probabilities of recurrence and the ultimate prognosis may be answered with reasonable accuracy. Briefly the classification of astrocytoma which Alpers and Rowe have proposed is as follows:

I. Fibrillary
   1. Solid
      (*a*) Piloid
      (*b*) Diffuse
   2. Cystic

II. Giant cell

III. Cellular

The division of astrocytoma into these three groups serves a definite practical purpose. It indicates, first of all, the great preponderance of the fibrillary group and makes possible in the majority of instances a safe prediction of the course

which the tumor will take. In general, tumors of the fibrillary groups grow slowly and have a correspondingly slow clinical course. The piloid subgroup of the solid fibrillary group, while benign histologically, seems to be less benign in clinical features. Tumors of the giant cell and cellular groups grow more rapidly and correspondingly follow a more rapid clinical course than those of the fibrillary group. The large main group of astrocytoma, the fibrillary group, is in good agreement with the investigations of others (Cushing and Bailey; Hortega; Roussy and Oberling). Penfield classified his fibrillary group as the piloid group. It has been the experience of Alpers and Rowe, however, that the piloid type of tumor is better regarded as a subdivision of the larger fibrillary group. Only 26 of the 112 fibrillary tumors collected by Alpers and Rowe could be regarded as piloid, with the features described by Penfield: (*a*) long fibrils arranged in bundles and (*b*) a few elongated cells having some but not all the features of classic astrocytes. Since the type cell in these tumors is the astrocyte, and since, also, the outstanding characteristic of the group is the presence of neuroglia fibrils, it has seemed to the authors that these tumors are best regarded as representing a fibrillary type of astrocytoma with special histologic characteristics but not with pathognomonic clinical features. Most of the tumors in the fibrillary group are characterized by the diffuse interlacing neuroglial carpet, which simulates the neuroglial arrangement in the normal white matter. The reason for the difference in appearance of these slowly growing tumors must remain at present a matter of speculation: Whether it is due to a difference in the inherent properties of the astrocytes or to the effects of exogenous stimuli carried to the cells by the blood is not clear. Nor is it clear why the number of fibrils within the tumors of the fibrillary group varies so greatly; why, for example, there are many fibrils and few cells in some tumors and many cells but few fibrils in others. In the former group the number of fibrils is so great that, while it is conceivable that they have been deposited by the few cells which lie among them, it is hard to dismiss the possibility of their formation from some other source. A similar preponderance of fibrils over cells is seen in some cases of fibroblastoma and in certain cases of gliosis in the brain. Granting that the preponderance of fibrils is due entirely to their formation by the cells, it is still not evident what the stimulus is for their being so heavily deposited in some tumors as compared with others, nor why some of these tumors develop as the diffuse type and others as the piloid type, all of them being the product presumably of the same cell, the fibrillary astrocyte. No attempt has been made to divide astrocytoma into fibrillary and protoplasmic types. In all the fibrillary tumors it is possible to find protoplasmic types of astrocytes as well as immature forms. It may be argued that the cellular form of astrocytoma which the authors have described is in reality the protoplasmic type, but even in this form there is some fibrillar formation. Since it is not clear whether the lack of fibrils is due to the presence of protoplasmic astrocytes or to the presence of immature cells, it has been deemed best to refer to these tumors as cellular astrocytoma. Similarly there is little doubt that the giant cell growths constitute a group in themselves. In appearance and structure they are quite different from the other groups.

FROM AUTHORS' SUMMARY. [ARCH. PATH.]

MELANOBLASTOSIS AND MELANOBLASTOMA: AN ANATOMIC STUDY. M. M. KESSLER, Am. J. Cancer **30**:19, 1937.

There are benign and malignant conditions involving melanoblastic cells. The benign conditions are congenital allotments of cells with melanoblastic functions to certain superficial tissues, the skin and its derivatives. This may be considered a normal distribution, as in the skin of the Negro, or a heterotopic one, as in the case of pigment cells found in the cerebrospinal meninges. The malignant conditions

arise from sarcomatous or carcinomatous changes in these cells wherever they are situated. The melanoblastic cells arise from both ectodermal and mesodermal tissues. The following classification of melanotic conditions is suggested:

I. Non-neoplastic

1. Mesodermal melanoblastosis: A normal, though heterotopic, incidence of mesoblastic melanoblasts in sufficient numbers to produce noticeable discoloration of the structure involved. Example: Pigmented cells in the meninges.
2. Epithelial melanoblastosis: A normal incidence of epithelial melanoblasts in sufficient numbers to be noticeable. Example: Skin of the Negro; epithelial inclusions in the brain.

II. Neoplastic

1. Benign
   (*a*) Mesodermal melanoblastoma: A slowly proliferating (or quiescent) discrete accumulation of mesodermal melanoblasts in any of the sites wherein such cells are normally found. Example: The blue nevus of Jadassohn; also, an accumulation of such cells within the brain or meninges in circumscribed nodular collections.
   (*b*) Epithelial melanoblastoma: A slowly growing or quiescent discrete proliferation of epithelial melanoblasts occurring in any of the situations in which such melanoblasts are normally found. This group name may be modified by the term "nevoid" whenever the specialized nevus cell is met, or by "basal cell" if the growth chiefly involves this cell. Example: The ordinary brown fleshy mole encountered on the face.
2. Malignant
   (*a*) Melanosarcoma: A rapidly proliferating, usually widely metastasizing melanin-forming tumor which answers the pathologic criteria of a malignant tumor arising in connective tissue. Example: A pigmented tumor arising in the choroid of the eye.
   (*b*) Melanocarcinoma: A rapidly proliferating, usually widely metastasizing melanin-forming tumor which answers the pathologic criteria of a tumor arising in epithelial tissue.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

A REVIEW OF PHYSICO-CHEMICAL STUDIES IN EPILEPSY. M. BROWN and H. A. PASKIND, Am. J. Psychiat. **93**:1009 (March) 1937.

There have been in the past few years many studies on epilepsy from the physicochemical point of view. Sixty-one contributions are reviewed in this paper. The authors conclude that while in the future important knowledge along this line may be added to present concepts of this mysterious syndrome, studies to date have thrown little light on the causes, pathogenesis and pathologic physiology of epilepsy.

JAHR, Omaha.

STUDIES IN ENDOCRINE THERAPY IN EPILEPSY. C. STEIN, Am. J. Psychiat. **93**:1181 (March) 1937.

Sixty-eight epileptic persons were studied by Stein, beginning in 1933. This report deals with 12 patients, whose cases complete the series. Stein concludes that in selected cases of epilepsy thyroid medication, if carefully controlled, is of some value in improving the general condition of the patient, thereby raising the convulsive threshold.

JAHR, Omaha.

Mode of Onset of Epilepsy. Joseph L. Fetterman and Volta R. Hall, Arch. Neurol. & Psychiat. **38**:744 (Oct.) 1937.

The authors studied the mode of onset in 160 cases of chronic convulsive disorders. In 75 or 80 per cent of cases the initial symptom is a convulsive seizure; and in from 20 to 25 per cent there is a mild disturbance resembling petit mal or an aura. There does not seem to be any striking correlation between the mode of onset and the type of epilepsy, the intelligence quotient of the patient, the family history or the course and severity of the disease.

Beverly, Chicago.

Necrotizing Encephalitis Simulating Tumor of the Brain Clinically and Due to Necrotizing Angiitis: A Clinicopathologic Report. Norman A. Levy, Arch. Neurol. & Psychiat. **38**:775 (Oct.) 1937.

The author reports the case of a 10 year old boy in whom physical signs suggesting tumor of the brain developed. He was found to have an unusual type of diffuse encephalitis due to an inflammatory process primarily of the blood vessels.

Beverly, Chicago.

Water Metabolism in Relation to Convulsions. Theodore T. Stone and Herman Chor, Arch. Neurol. & Psychiat. **38**:798 (Oct.) 1937.

The relationship of the water balance to major convulsions was investigated. The patients were all hospitalized, the intake and outgo of fluids measured and careful analysis of the blood made. It was found that a high intake of fluids for forty-eight hours, with or without ingestion of ampules of pitressin, did not produce any increase in the number of convulsions. No evidence was found of increased retention of water before convulsions or of any influence on convulsions of markedly restricting the intake of fluids for short periods (forty-eight hours). The work was done on young adults.

Beverly, Chicago.

Infantile Tetany. Joseph Dolce, Arch. Pediat. **54**:560 (Sept.) 1937.

A case is reported.

Orr, Buffalo.

Otogenic Streptococcic Meningitis. Abraham M. Litvak and Marjorie B. Klughertz, Arch. Pediat. **54**:714 (Dec.) 1937.

In recent years there has been an increase in the number of reported cases of recovery from streptococcic meningitis. Seventy-seven recoveries occurred within the last five years, as compared with 46 recoveries in the preceding thirty-one years. In 1937 recovery was recorded in 32 cases. In 15 of these sulfanilamide or a derivative was used.

The writers report the case of a 7½ year old girl who recovered completely from streptococcic meningitis of otitic origin. The spinal fluid showed hemolytic streptococci on smear and culture seventeen times. Mastoidectomy was performed, and concentrated scarlet fever antitoxin and autogenous blood serum were administered intrathecally. The patient was discharged after forty-nine days in the hospital. Examinations one and two months after discharge failed to reveal any residual signs or complications.

Orr, Buffalo.

Relapsing Facial Paralysis in the Same Family. Evelyn Johnson and Albert V. Stoesser, Arch. Pediat. **54**:726 (Dec.) 1937.

Two cases of relapsing facial paralysis in the same family are reported. Otitis media may have been an etiologic factor.

Orr, Buffalo.

CYTOPLASTIC BODIES IN A CASE OF MEGALENCEPHALY. ABNER WOLF and DAVID COWEN JR., Bull. Neurol. Inst. New York **6**:1 (Jan.) 1937.

A boy of 13 months died of pneumonia. Clinically he showed mental retardation, muscular weakness and hydrocephalus.

A section of the cerebrum showed no gross abnormalities. The cortex was of normal thickeness, and there was slight congestion of the white matter. There was no hydrocephalus.

Microscopically, there were changes in the deeper layers. There was complete chromatolysis throughout. Most of the ganglion cells were pale; many were swollen, and nearly all contained vacuoles of varying sizes. In most instances there were bands of rarefaction of the cytoplasm. Within the vacuoles were dark blue structures.

The large size of the head and the increased weight of the brain were due to true megalencephaly. The size was due to the swelling of the ganglion cells and of the oligodendroglia. The cytoplasmic bodies were considered to be due to a toxic action probably of a virus, on the cells. BEVERLY, Chicago.

THE ETIOLOGY OF HEADACHE: II. THE OCCURRENCE AND SIGNIFICANCE OF HEADACHE DURING VENTRICULOGRAPHY. EARL D. BREWER, Bull. Neurol. Inst. New York **6**:12 (Jan.) 1937.

"In a large number of instances, introduction of air into the ventricles by direct ventricular puncture does not cause headache. In the cases in which headache is produced, it is often seen to appear upon the withdrawal of fluid, and to be relieved by the injection of air. . . . Headache occurred as often in patients who did not have as in those who did have an intracranial neoplasm. . . .

"The fact that headache occurred when fluid was removed from a ventricle, and was relieved by the injection of air makes it probable that there is a mechanical factor in the production of the headache and that this is an alteration of intraventricular pressure. Whether the headache can be explained on the basis of a change of pressure in the lateral and third ventricles or of a change of pressure in the third ventricle is uncertain." BEVERLY, Chicago.

A STUDY OF SUGAR TOLERANCE TESTS IN TWO HUNDRED PATIENTS WITH CONVULSIONS. HENRY H. DREWRY, Bull. Neurol. Inst. New York **6**:62 (Jan.) 1937.

A study was made of 200 cases of convulsions to determine the relationship of the manifestation to hypoglycemic states. The sugar tolerance test produced a curve with a peak below 150 mg. per hundred cubic centimeters for 93, and below 120 mg. for 27. For 3 patients the sugar content of the blood was below 50 mg.; all these had adenoma of the pancreas. For 24 the sugar content at one time or another was between 50 and 70 mg.; none of these showed definite symptoms of hypoglycemia at the time the blood was taken. BEVERLY, Chicago.

THE SENSE OF SMELL: XV. A NOTE ON THE VALUE OF TESTS OF OLFACTORY ACUITY FOR THE DIAGNOSIS OF PITUITARY TUMOR. CHARLES A. ELSBERG and JANE STEWART, Bull. Neurol. Inst. New York **6**:126 (Jan.) 1937.

In an analysis of the olfactory acuity of 40 patients with pituitary adenoma, meningioma or aneurysm of the internal carotid artery, changes were found in 29. In cases in which there was uncertainty about the tumor, the results of tests of olfactory acuity were an aid in the differential diagnosis. BEVERLY, Chicago.

WOOD TICK PARALYSIS IN CHILDREN. E. J. BARNETT, J. A. M. A. **109**:846 (Sept. 11) 1937.

Wood tick paralysis in children is an acute, afebrile and progressive disease. The child collapses when he attempts to stand; when he is aided his gait is ataxic, and finally he is unable to walk or stand with support. While the tick, which

has been feeding on the human host for six days, may be found anywhere on the body, the occipital region is the most usual site. Prompt but gentle removal of the tick is followed by rapid improvement and complete recovery in forty-eight hours. Delayed removal results in death in most cases from respiratory paralysis. The disease is relatively unknown to physicians and is usually confused with the ascending type of acute polioencephalitis. Experimental evidence suggests that the disease is due to a poison liberated from the eggs of the tick and that it develops at the time of the formation of the eggs. Further research is necessary to establish more definite knoweldge about the disease and its cause. It is recommended that this disease be given more time and space in textbooks and by instructors in pediatrics.

BONAR, Salt Lake City.

MULTIPLE SCLEROSIS SYNDROME IN A CHILD: REPORT OF A CASE. D. M. OLKON, J. Nerv. & Ment. Dis. **85**:139 (Feb.) 1937.

A 14 year old Swedish girl complained of a progressive difficulty in walking from which she had suffered since the age of 6 years. The history was that of normal development until this time, with no serious illnesses preceding the onset of the symptoms. At the time of admission she showed absence of abdominal reflexes, a spastic gait, rigidity, active knee and achilles tendon reflexes, ankle clonus, Babinski, Oppenheim and Chaddock signs and Rossolimo's reflex. There was no sensory involvement, and serologic tests were negative.

JAHR, Omaha.

APPLICATION OF A MODIFIED DEHYDRATION RÉGIME TO INSTITUTIONALIZED EPILEPTICS. E. A. WHITNEY, J. Nerv. & Ment. Dis. **85**:283 (March) 1937.

Dehydration has for some time been recognized as efficacious in the treatment of epilepsy, particularly when combined with other accepted therapeutic methods. While dehydration is accompanied as a rule by some difficulties, the results usually justify its employment in institutional patients. In this study Whitney brings out the following facts: 1. Dehydration decreased the severity as well as the frequency of the seizures. 2. Both the severity and the frequency of seizures increased when dehydration was discontinued. 3. In eight of the 9 patients employed in this study there was a gain in weight. 4. There was no appreciable change in the mental condition of the patients, except that attention and initiative performances were raised during the period of dehydration. 5. Even those epileptic patients who had low grade mental defects showed some improvement resulting from the restriction of fluids.

JAHR, Omaha.

OBESITY FOLLOWING CHOREA. P. R. EVANS, Brit. J. Child. Dis. **34**:179 (July-Sept.) 1937.

Obesity following an attack of chorea is probably not uncommon, even though reports of this sequela are not numerous. The distribution of fat over the abdomen and pelvis, the shoulders, the cheeks and the proximal segments of the limbs is common to postchoreic obesity, "idiopathic" obesity and Fröhlich's syndrome.

Evans stated that it is unlikely that prolonged rest and good feeding cause the obesity in association with this condition. Two cases are described, in one of which there were profuse striae atrophicae.

Obesity of the distribution observed in these cases occurs with chromophobic or basophilic adenoma of the pituitary, suprapituitary tumor and internal hydrocephalus from any cause, after encephalitis of various types and as an idiopathic condition.

It is suggested that the obesity following rheumatic chorea may be regarded as postencephalitic, possibly associated with degeneration in the suprapituitary region.

Treatment seems to be rather unsatisfactory, although a diet low in carbohydrate may be useful.

LANGMANN, New York.

DIAGNOSIS OF CHRONIC SUBDURAL HEMATOMA OF TRAUMATIC ORIGIN. G. S. HALL, J. Neurol. & Psychopath. **17**:26 (Jan.) 1937.

This is a discussion of 4 cases of chronic subdural hematoma and 1 case of traumatic intravertebral hematoma. The age range of the patients was from 5 months to 82 years. Damage from intracranial pressure due to subdural changes varies inversely with the age of the patient: The earlier in life hemorrhage develops, the more frequent and severe is raised intracranial pressure.

JAHR, Omaha.

THE CEREBRAL CIRCULATION: SOME NEW POINTS IN ITS ANATOMY, PHYSIOLOGY AND PATHOLOGY. T. J. PUTNAM, J. Neurol. & Psychopath. **17**:193 (Jan.) 1937.

The cerebral arteries are not end arteries. They possess a rich anastomosing system. The vulnerability of the brain toward vascular disturbances is due to the sensitiveness of the parenchyma rather than to the deficiency in the blood supply. The cerebral vessels bear nerves and are under vasomotor control by the sympathetic system. A comprehensive review of the recent literature, with a practical clinical interpretation of the experimental findings, is submitted together with a discussion of the subject in general.

JAHR, Omaha.

ABSORPTION OF ULTRAVIOLET RAYS BY CEREBROSPINAL FLUID. E. F. SKINNER, J. Neurol. & Psychopath. **17**:213 (Jan.) 1937.

This paper deals with spectrophotometric examination of cerebrospinal fluid in a series of 50 cases of meningeal or cerebral lesions, with the following results: Tuberculous meningitis gave rise to a characteristic change in the spectral curve as did also dementia paralytica, though in the latter the change was not so striking. During the course of a disease the curve tended to become steeper if progress was toward fatality. Most cerebrospinal fluid shows absorption of the ultraviolet rays between wavelengths of 2,600 and 3,200 angstroms, which gives a humped curve on the graph. In acute or chronic infection of the meninges the normal curve is shifted toward the long wave end of the spectrum.

It is thought that the hump in the normal curve may be due to uric acid and that the shift to the right in the inflammatory conditions may be due to an increase in this constituent.

JAHR, Omaha.

HEREDITARY GENERAL PARALYSIS. L. BABONNEIX, J. SIGWALD and GISSELBRECHT, Bull. Soc. de pédiat. de Paris **34**:752 (Dec.) 1936.

A girl 10 years of age had shown evidence for a year of dementia paralytica and mental disturbance due to congenital syphilis.

BENJAMIN, Montreal, Canada.

ACUTE OPTIC NEURITIS AND MYELITIS AND INTERCURRENT VARICELLA, TREATED BY FIXATION ABSCESS AND IODOBENZOMETHYLFORMINE SALICYLATE; CURE WITHOUT SEQUELAE. L. BÉTHOUX, R. ISNAL and J. MARCOULIDÈS, Bull. Soc. de pédiat. de Paris **35**:199 (March) 1937.

A 6 year old girl showed neurologic signs and optic neuritis. She began to have some weakness of the lower extremities about two months before she presented varicella. This disease was of its usual mild nature and cleared up promptly, so that it apparently had nothing to do with the fact that the neurologic condition became worse. Recovery was complete eight months after the onset of the illness. Whether there exists a neurotropic virus which is responsible for this type of infectious encephalomyelitis or whether it may be produced by a number of infectious agents is not known.

BENJAMIN, Montreal.

FOUR CASES OF FRIEDREICH'S ATAXIA WITH MENTAL SYMPTOMS IN MEMBERS OF THE SAME FAMILY. E. DE SMET, A. DE WULF, DYCKMANS and L. VAN BOGAERT, J. belge de neurol. et de psychiat. **37**:155 (March) 1937.

Mental impairment in cases of Friedreich's ataxia is not unusual, but most authors believe that psychoses are uncommon. De Smet and his co-workers report four cases of Friedreich's ataxia occurring in two families, in each of which there were cases of dementia praecox. No definite hereditary relationship was found between the two conditions. The mental symptoms usually appeared several years after the onset of the involvement of the spinal cord and cerebellum.

WAGGONER, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

SYNDROME OF POLYRADICULAR NEURITIS OF GUILLAIN AND BARRÉ OCCURRING IN A CHILD. J. ANSAY, J. belge de neurol. et de psychiat. **37**:311 (May) 1937.

Ansay reports a case of polyradicular neuritis with albuminocytologic dissociation in the cerebrospinal fluid, which occurred in a child aged 8 years. The only residual signs were slight weakness of the muscles supplied by the peroneal nerves and a slight valgus deformity of each foot. Few cases of this syndrome occurring in children have been described; this is the fifth case in which typical findings are reported. The syndrome of Guillain and Barré is a definite entity, clinically and serologically; numerous cases have been observed in adults. The causes of the condition are not known. Most authors believe that a toxic or toxic-infectious agent may produce the same picture.

WAGGONER, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

ARM-EXTENSION REFLEX IN YOUNG INFANTS. J. ZÁDOR, Rev. neurol. **66**:742 (Dec.) 1936.

Between the ages of 3 and 5 months an infant shows a reflex which seems to be a measure of motor evolution. Lying on his back, he is lifted by the arms so that his head is just clear of the table. When he is released suddenly, the arms go into extension as soon as the head touches the table. There is no flexion of the arms, and the legs remain unchanged in position.

DAFFINEE, Boston.

TWO CASES OF FAMILIAL CEREBELLOATAXIC IMBECILITY. B. STOKVIS, Psychiat. en neurol. bl. **1**:206, 1937.

Stokvis reports the cases of two patients, a brother and sister, whose grandfather had epilepsy and whose two paternal uncles were drunkards. A third sibling was "almost insane." Both the patients were late in learning to walk and talk. Disturbances in coordination become evident at the end of the first year. Although signs of cerebellar involvement prevailed in the clinical picture, other phenomena, such as a bilateral Babinski sign, were inconsistent with the diagnosis of pure cerebellar disease. Both patients showed evidences of imbecility and numerous schizophrenic traits, such as hallucinations, grimacing and negativistic and catatonic behavior. Both the physical and the mental abnormalities are attributed to the same hereditary cause.

LEWY, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

RELATION OF PREMATURE DELIVERY TO CERTAIN CEREBRAL DISTURBANCES. T. BRANDER, Finska läk.-sällsk. handl. **80**:134 (Feb.) 1937.

Brander studied the effect of premature delivery on the intelligence. He found in a series of 370 premature children that 1.4 per cent had an intelligence quotient above normal, 46 per cent a normal quotient and 52.7 per cent a quotient below normal. The main factors leading to mental deficiency were low weight at birth, complications of birth and hereditary psychic taints. The less marked forms of mental defectiveness are fully as important as the gravest forms, particularly as persons with the former are more detrimental to society than the hospitalized idiots.

EGHAMMAR, Chicago.

Diseases of the Genitourinary Tract

GRANULOSAL CELL TUMORS OF THE OVARY: REPORT OF THREE RECENT CASES. J. V. MEIGS and L. PARSONS, New England J. Med. **216**:681 (April 22) 1937.

A granulosal cell tumor, follicle cell tumor or oophoroma folliculare is a tumor composed of cells that resemble very closely the cells of the granulosa of the normal graafian follicle. Like the cells of the follicle, the tumor cells are capable of secreting estrogen.

The granulosal cell tumor may be of almost any size, from 1 mm. to 20 or 30 cm. in diameter, but the size is usually about that of a lemon or an orange; the growth is nearly always unilateral. It is usually a solid tumor with cystic areas in it, and there is a characteristic yellow tinge to the tumor tissue, some areas being more yellow than others.

The presence of such a tumor in a young person usually causes precocious genital development, owing to an excess of estrogen. The patient menstruates early, and the periods are irregular and anovulatory. The breasts are well developed, and other secondary sex characteristics are present early. Removal of such a tumor restores normal development.

Granulosal cell tumors should be operated on and removed. These lesions are rarely bilateral, are usually benign but may be malignant.

GENGENBACH, Denver.

TREATMENT OF CRYPTORCHIDISM. H. BJERRE, Ugesk. f. læger **99**:513 (May 13) 1937.

Bjerre reports on the results of operations to correct 251 retained testes in 196 patients. Half of the patients were past puberty. A follow-up study showed that the anatomic result was good in 58 per cent, bad in 32 per cent and bad with atrophy of the testes in 10 per cent. The prognosis is better if the retained testis is movable and can be replaced into the scrotal sack. As to the relation of the prognosis to the age of the patient at the time of operation, it was found, with due consideration being paid to different degrees of retention, that the chance for success is twice as good if the operation is done before puberty than later and that there is no distinct difference between age groups in this respect during childhood. Postoperative atrophy of the testis depends on a lowering of the vitality of the organ by forced displacement and impairment of the blood supply. Such forced displacement should never be employed. Bilateral replacement should preferably be done at two sittings with a six month interval. The operative results are compared with those in 188 patients who were not operated on. Of the 188 patients, 119 (63 per cent) showed a spontaneous descent. In 13 cases in which the testes were movable there was spontaneous descent. The descent occurred before the age of 15 years. The relation of fertility to cryptorchidism was studied in 24 cases of bilateral cryptorchidism. In 4 of the patients there was a spontaneous descent, and all 4 were fertile. Of the 15 patients with bilateral cryptorchidism operated on with good anatomic result, 9 were fertile. Of the 5 with bilateral cryptorchidism treated surgically but with bad anatomic result, all were unfertile. The hypoplasia of the testis in cryptorchidism is to be regarded as independent of the retention, because even when the anatomic result is good there may be sterility. The author suggests that it is best to postpone an eventual surgical treatment until puberty except in cases in which the condition is complicated with inguinal hernia or in which there are pains in the retained testis. Treatment with gonadotropic substances may be tried in cases in which the external genital organs are dystrophic.

WALLGREN, Göteborg, Sweden.

Diseases of the Ductless Glands; Endocrinology

OBSERVATIONS ON THE SITE OF THE ANTAGONISTIC ACTION OF POSTERIOR PITUITARY EXTRACTS ON INSULIN HYPOGLYCÆMIA. H. COHEN and J. LIBMAN, Quart. J. Med. **6**:157 (April) 1937.

The authors studied the arterial-venous differences in blood sugar in a group of normal persons after oral administration of 50 Gm. of dextrose and after combined administration of dextrose and an extract of the posterior lobe of the pituitary. The combined administration of dextrose and the extract produced a more marked and prolonged rise in the blood sugar than that following administration of an equivalent amount of dextrose by mouth. When the effect of the extract of the posterior lobe of the pituitary on the dextrose tolerance curve is marked, the arterial-venous differences are diminished.

The authors concluded that extracts of the posterior lobe of the pituitary antagonize the hypoglycemia due to administration of insulin by retarding the peripheral utilization of the blood sugar.

BRADFORD, Rochester, N. Y.

INFANTILE DIABETES. E. A. BERETERVIDE, J. J. REBOIRAS and R. BEAUTEMPS, Arch. argent. de pediat. **8**:583 (July) 1937.

The dose of insulin varies, depending on the clinical symptoms and their development in a given case. Usually two or three, at the most four, injections are required. The diabetic infant will seldom survive without insulin.

Practically all infants with diabetes, especially if the disease is severe, present distinct glycemic curves, and in the individual infant the curves at dfferent hours will vary.

Proper adjustment of the insulin dosage and of the time of meals will correct the diabetic state in most subjects or will keep it controlled within normal bounds.

SCHLUTZ, Chicago.

THE FUNCTION OF THE THYMUS AND WATER METABOLISM. Y. HIRATA and T. OKAMOTO, Orient. J. Dis. Infants **21**:48 (May) 1937.

The data on the normal water content of the erythrocytes, blood plasma and the liver of the healthy rabbit may be summarized as follows:

	Total Water (%)	Combined Water (%)	Free Water (%)
Erythrocytes	72.2	28.62	43.6
Blood plasma	92.1	14.74	77.4
Liver	72.8	30.36	42.4

In thymic hypofunction induced either by roentgen irradiation or by extirpation of the gland, the decrease in combined water in all the aforenamed tissues, as well as in body weight, is demonstrable. Opposite results are produced by hyperfunction of the thymus induced either by injections of an extract of thymus gland or by peroral administration of calf thymus. If roentgen irradiation of the thymus is accompanied by administration of thymus gland extract no decrease in the combined water or in the body weight results. By continuous administration of water alone there results an increase in combined water but no change in the body weight. If continuous administration of water is combined with injections of gland extract the increase in combined water is distinctly noticeable. From these observations the authors conclude that the combined water content bears a close relation to the thymic function, the two paralleling and depending on each other, and, furthermore, that continuous administration of water leads to an increase in the combined water content of the tissues.

KATO, Chicago.

A Case of Juvenile Hyperparathyroidism? J. Hellström, Nord. med. tidskr. **13**:595 (April 10) 1937.

A girl of 11 years was observed who had the following symptoms: wasting, secondary anemia, a general decrease in the calcium content of the osseous system, numerous decalcified foci localized inter alae in the skull, hypercalcemia (17.5 mg. per hundred cubic centimeters), an increase in the excretion of calcium in the urine (from 0.3 to 0.4 Gm. per day) and polyuria. The disease was considered to be hyperparathyroidism, and in order to extirpate the eventual parathyroid adenoma the girl was operated on. No parathyroid adenoma was found at the usual site or in the upper part of the mediastinum. The inferior thyroid artery was ligated, without improvement in the condition. The possible relation between this somewhat obscure condition and the Schüller-Christian disease is discussed.

Wallgren, Göteborg, Sweden.

Diseases of the Muscles, Bones, Joints and Lymph Nodes

Radiographic Check on the "Sign of Reduction" in Congenital Dislocation of the Hip. G. Castagnari, Lattante **8**:438 (July) 1937.

The "sign of reduction" is the bouncing sensation felt and frequently seen when reduction of the dislocation is attempted by the method of Lorenz. It is more easily demonstrated in true luxation of the hip than in preluxation. In 49 of 54 cases in which this sign was obtained roentgenograms showed reduction of the dislocation.

Higgins, Boston.

Role of Trendelenburg's Sign in Diagnosis of Congenital Dislocation of Hip. P. Puky, Arch. f. klin. Chir. **190**:390 (Oct.) 1937.

A child of 21 months showed apparent lengthening of the right leg and difficulty in walking. On the basis of measurements and the absence of a Trendelenburg sign, congenital dislocation was ruled out. At the age of 5 years she was seen in the author's clinic, where roentgenograms disclosed a dislocation of the left hip. The bones of the left leg were markedly hypertrophied, which produced the discrepancies observed clinically. The author feels that the presence or absence of the Trendelenburg sign is not trustworthy and that roentgen examination should be used in any case in which there is a suspicion of congenital dislocation of the hip.

Daffinee, Boston.

New Roentgen Signs for Differentiation Between Epiphysial Separation and Dislocation of the Hip in Infancy. H. O. Kleine, Klin. Wchnschr. **12**:629 (April 22) 1933.

Beginning with the second half year of life, a dislocation of the hip joint shows in the roentgenogram hypoplasia of the center of ossification in the head of the femur and of the entire proximal portion of the shaft of the femur. In epiphysial separation resulting from obstetric injury, the roentgenogram reveals temporarily hyperplasia of the center of ossification in the head of the femur and in general acceleration of the growth process in all epiphysial nuclei that are near the separation. A similar acceleration of epiphysial growth can be observed also in other fractures near the epiphysis occurring during infancy.

Silverman, Syracuse, N. Y.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

C. A. ALDRICH, M.D., *President*

Regular Meeting, March 15, 1938

GEORGE F. MUNNS, M.D., *Secretary*

CONGENITAL MEGACOLON. DR. ALFRED D. BIGGS and DR. GÉZA DE TAKÁTS.

Congenital megacolon was popularized by Hirschsprung in 1886, although it had previously been described by more than twenty authors. A complete bibliography may be found in collective reviews by Finney in 1908, Ask-Upmark in 1930 and others. The incidence is usually given as from 1 in 10,000 to 1 in 20,000, and the prevalence of male over female patients, as 4 to 1.

Many theories, both anatomic and physiologic, have been advanced to explain the cause of congenital megacolon. In recent years, opinions center around neuromuscular dysfunction.

The diagnosis of congenital megacolon, except when the condition is found in an infant, is easily made; it depends on three cardinal symptoms: obstinate constipation, marked enlargement of the abdomen and visible peristalsis. In the newborn period the diagnosis may be difficult. Diarrhea may be persistent or may alternate with constipation during the first weeks of life. Persistent vomiting is likely to occur at this time. In later childhood, vomiting seldom occurs.

In undertaking medical management one must assume that congenital strictures are absent or that if present they have been dilated. A large number of methods of treatment of congenital megacolon have been suggested, and a large number of drugs have been advised. In our experience, warm colonic flushings, administration of mineral oil, systematic rectal dilations and the giving of a well balanced diet have been found most helpful.

As a preoperative test of the possible effect of sympathetic denervation on the emptying of the bowel, spinal anesthesia has been advocated. It has been noted in some cases that spinal anesthesia alone will restore functional activity for months.

All patients up to the age of 3 or 4 years should be treated medically; all with mild and latent conditions which respond to therapy should be kept under medical management.

The high mortality following resection of the bowel and the frequency of recurrences have discouraged surgical treatment of megacolon. However, with the introduction of sympathectomy many of the objections to surgical procedure have been removed.

DISCUSSION

DR. GÉZA DE TAKÁTS: When one is deciding between medical and surgical management, several factors have to be taken into consideration. Obviously the age of the patient is important. I do not believe that any surgeon would want to undertake extensive resection of the bowel or sympathectomy before the age of 3 or 4 years unless perforation of the bowel or volvulus of the sigmoid flexure or of the cecum were impending, or unless intestinal stasis were so intractable that colostomy might be required to save the life of the child. In our experience, high colonic flushings have served better for relief of the obstruction. The most frequent cause of acute obstruction is the long sigmoid loop, though not all patients have this abnormality. Even after sympathectomy the loop persists and is a cause

of trouble. We do not want to give the impression that sympathectomy has replaced colectomy, because the latter will always constitute a mechanical factor. Some children have just a dilatation of the sigmoid flexure; some have total colonic dilatation. Surgical treatment of course differs according to the condition. It is much more extensive when the entire colon is involved.

The mortality following colonic resection in the past has been so high—and this includes not only immediate mortality but later mortality—that the surgeon is happy to have patients with megacolon treated by the pediatrician, although most pediatricians are glad to refer them to the surgeon. Ask-Upmark tabulated 102 cases from Swedish hospitals and showed that surgical intervention caused a higher mortality than nonsurgical treatment; no instances of sympathectomy were included. The most disconcerting thing about colonic resection is not the mortality, which should not exceed 6 or 8 per cent, but the fact that the disease recurs. Obviously, partial removal of the colon has not touched the cause. Therefore, since the first sympathectomy was performed by Wade and Royle, of Australia, ten years ago, great interest has been focused on this form of treatment.

In a case in which sigmoidectomy had been done six years previously, the colon had lost its tone and was excessively large, being dilated to five times normal size. The anastomosis could be seen under the fluoroscope. The patient, a woman who is now 21 or 22 years of age, had not lost the colonic distention. We may say that considerable help has been given but that the long sigmoid will always produce trouble. Sympathectomy is now being considered.

In order to understand the rationale of these sympathectomies, a diagram has been prepared. The lumbar outflow goes through the sympathetic chain, passing through the hypogastric plexus to the bowel, tightening the sphincter and relaxing the bowel. There is adequate experimental proof of this. The parasympathetic outflow comes through the third and fourth sacral segments and may be easily injured during visceral resection. It contracts the descending colon and opens the sphincter. There is a third set of somatic nerves, which are motor and sensory to the anus, and a fourth group, the intramural plexuses.

Hurst has stated the belief that when fecal matter passes into the rectum the normal response is relaxation of the sphincter. When for some reason the intrinsic intramural mechanism is disturbed, the fecal mass will be impacted; yet there is no desire to defecate. One can give some children 3 or 4 quarts (2.8 or 3.8 liters) of fluid containing barium sulfate, yet they have no desire to defecate. After sympathectomy, perhaps an increase in tone results, so that they readily expel the barium. Occasionally, when spinal anesthesia cannot be obtained and it is not desirable to put the child to sleep, the same effect can be produced by injecting a drug that has a parasympathetic action.

In 1 case spontaneous function returned after six months; it is amazing that it returned at all, as the contractility of the bowel was so poor before the operation.

I should like to say a word about the mortality in cases in which sympathectomy was done. So far more than 100 patients have been operated on for megacolon: of these, 2 have died. The procedures were extensive splanchnic resections. Some types are preferably done in two stages. In our own series of cases we have performed lumbar sympathectomy on 48 patients and have lost 1, who does not fit into this discussion. He was a middle-aged man with Buerger's disease, who had coronary thrombosis on the fifth postoperative day.

I should like to emphasize that when megacolon is treated in young infants and older children, every effort should be made to decompress the bowel, first, because one may effect a cure and, second, because any persistent distention of the colon will lead to loss in muscular power. Owing to this loss, any later attempt at sympathectomy will be useless, and the flow of blood to the bowel will be so impaired that much material will be absorbed through the lymphatic vessels. Dr. Finney expressed the opinion that lymphadenitis is the primary cause of megacolon, but it may be that instead of being the cause it is the result. There is pretty good evidence of that: Dye or bacteria placed in a distended colon will pass through the lymphatic vessels.

DR. JOSEPH BRENNEMANN: I have been much interested in this subject for many years. I have been impressed with the fact that I have seen few cases of megacolon due to Hirschsprung's disease as compared with the number in which the ailment was due to some other condition. If one uses the term Hirschsprung's disease in the original sense, it should include only cases of congenital idiopathic megacolon without distal obstruction, because in the cases that Hirschsprung reported in 1886 and 1888, he observed at autopsy no evidence of obstruction. Having seen so few instances of true Hirschsprung's disease, I have always wondered whether the patients that are reported to have this condition have intestinal patterning such as one sees with obstruction. Hirschsprung did not mention this point except to say that in 1 case there were *wechselnde Darmwindungen* (changing coils of intestine).

On the other hand, I have seen at least 20 patients with marked megacolon which was due to a tight fibrous obstruction just a little above the sphincter ani. Several of the strictures would not admit even a little finger for some time, but all ultimately yielded to digital dilation. Many of these patients presented enormous dilatation of the colon with extreme peristalsis. This condition apparently is due to a lack of complete fusion of the mesenteron and the proctodeum and has nothing to do with the sphincter. I saw a child several years ago who had an enormous megacolon that was instantly relieved when a proctoscope was inserted about 3 inches (8 cm.). The mother was given a proctoscope, which she used whenever it was needed; I understand that the child can now get along without this treatment.

DR. HENRY PONCHER: A recent abstract of some work by Robertson and Kernohan, which appeared in the *Proceedings of the Staff Meetings of the Mayo Clinic* for Feb. 23, 1938, may be pertinent to this discussion. When microscopic sections of the colon were examined by means of special stains, it was observed that the ganglion cells and fibers of the plexus of Auerbach were definitely smaller than normal and were vacuolated. It was stated that a similar appearance was noted in several other cases of Hirschsprung's disease. Whether these changes are cause or effect, they may be of importance in the course of Hirschsprung's disease. I am wondering whether Dr. de Takáts can explain the benefit of sympathectomy, assuming these changes to be present.

DR. ALFRED BIGGS: Hirschsprung's disease, as it is defined by him, cannot be due to a demonstrable mechanical obstruction. In one case it was fully expected that after the fibrous ring had been dilated the bowel would diminish in size. This did not happen. After a few weeks' treatment with periodic dilation it was demonstrated that the ring no longer existed. This made no difference in the progress of the disease. Therefore it was called true Hirschsprung's disease. This obstruction was of milder degree than those just described by Dr. Brennemann.

DR. GÉZA DE TAKÁTS: I think we all know what Dr. Brennemann has done and how strongly he has emphasized the great importance of rectal stricture. There undoubtedly was a mechanical factor in the cases of 2 children for whom sympathectomy was done, for peristaltic waves were seen, which suggested a mechanical obstruction. Yet neither digital examination nor a barium sulfate enema revealed any obstruction. There must be some mechanical factor; possibly this is angulation of the sigmoid loop because, as may be noted, with a long mesentery the more distention there is the more angulation occurs. When waves are contracting against a mechanical obstruction at the sigmoid flexure, it may be necessary to resect the flexure, even after sympathectomy.

In regard to Dr. Poncher's remarks, several authors have examined the myenteric plexuses by the newer histologic methods, but some of them did not find degenerative changes. One could explain these changes as the result, rather than the cause, of megacolon. If there is degeneration of the plexus, that bears out Hurst's contention that the fault lies in the failure of relaxation which is brought about by the diminished activity of such plexuses. Sympathectomy would help this in one way. It is known that there is a definite sympathetic inhibition

of the nerves supplying the bowel; if that is relieved it would be just enough to allow compensation by the antagonistic nerve supply. It has been found that in patients who were on exactly the same management before as after sympathectomy, physostigmine salicylate seemed to act after sympathectomy.

ADENOMA OF THE RECTUM IN CHILDREN: REPORT OF A CASE IN A THIRTY MONTH OLD GIRL. DR. MORTIMER DIAMOND.

Adenoma of the rectum in children is uncommon and has received little attention in the literature; yet its importance as a causal factor in rectal bleeding, prolapse of the rectum, abnormal discharge or constipation should be given consideration.

The following case report is presented because it brings out two important facts: 1. A rectal adenoma may produce marked constipation, which incorrectly may be treated as a symptom only. 2. Routine proctoscopic examination is important when there is any condition suggestive of pathologic change in the lower part of the colon or in the rectum.

A 30 month old girl was brought to the hospital because since birth she had suffered from increasing constipation and prolapse of a bleeding mass on defecation. Proctoscopic examination disclosed that the cause of the symptoms was a pedunculated adenoma in the rectum, 4.5 cm. above the pectinate line. In addition, there was a sessile adenoma in the sigmoid flexure of the colon, 11.5 cm. above the pectinate line. The rectal adenoma was 2.5 by 2 by 2 cm. and had a pedicle 1 cm. long. It had pulled the adjacent mucosa into a cone 3.5 cm. long, which added to the length of the pedicle and permitted the tumor to prolapse on defecation. Through the proctoscope the tumors were removed, and their bases were coagulated. Complete healing and relief from symptoms followed. Examination of microscopic sections of the tumors revealed them to be benign.

The condition in this case is unusual because the rectal adenoma was congenital and because it produced marked constipation.

Review of the 25 available case reports which are sufficiently complete to be utilized for comparison shows that the child usually is between 2½ and 10 years of age, the familial tendency is rare, the incidence is evenly divided between the sexes and in the majority of cases only one tumor is found. Bleeding is the most common symptom, being present in 95 per cent of the cases, and the passage of mucus is second in frequency, being found in 60 per cent. Prolapse of the tumor occurs in 33 per cent of the instances, while prolapse of the rectal mucosa was described by one observer only. Finally, the probability of malignant degeneration is small.

The present case is unusual because (1) the rectal adenoma was congenital; (2) it produced marked constipation and (3) it was accompanied by a sigmoidal adenoma.

IDIOPATHIC ULCERATIVE COLITIS IN INFANTS AND CHILDREN. DR. JOHANNA HEUMANN.

Idiopathic ulcerative colitis is a chronic inflammation of the large bowel, of unknown cause. It is characterized by superficial or deep ulceration, with constant or recurring bloody mucous diarrhea; it lasts from several months to several years. Apparently the disease possesses no infective properties. Involvement may be mild or severe. It is most common in young adults and is rare in infants. The pathologic changes consist of ulcerations in the rectosigmoid and descending portions of the colon, placed close together and leaving little mucous membrane unaffected. The onset is usually insidious. The first symptom noted is gradually increasing frequency of bowel movement, which is often accompanied by cramps and abdominal discomfort. Later, pus and blood appear in the stools, which may be as numerous as fifteen or more a day. The symptoms may continue for months or years. There may be remissions. Large hemorrhages seem to be frequent in children. The passing of blood in clots, rather than intimately mixed with

the mucus, is rather characteristic. Proctoscopic examination reveals a considerable amount of grayish mucopurulent material. When this is wiped away the mucous membrane appears red and granular, with minute ulcerations diffusely scattered over its surface. The mucous membrane bleeds easily. This is due not necessarily to ulceration but rather to diapedesis of the edematous, hemorrhagic, tense mucous membrane. Roentgen examination reveals disappearance of the normal haustra, narrowing of the lumen and later a pipelike appearance of the bowel.

The condition must be differentiated from (1) a number of bacterial intestinal infections, such as paratyphoid fever, gastroenteritis, dysentery and tuberculous enteritis; (2) parasitic infections such as amebic dysentery, balantidial dysentery and the infection with Lamblia intestinalis; (3) colitis complicating the course of another disease, such as severe rhinopharyngitis, angina, grip, bronchopneumonia, measles, scarlet fever, meningitis or lymphogranuloma venereum; (4) exogenous intoxication, as with mercury and arsenic, and endogenous intoxication, as with uremia, and (5) postoperative ulcerative colitis and, rarely, Meckel's diverticulum.

The prognosis is unfavorable: Recovery is invariably slow and rarely complete. Treatment is confused, and the results are disheartening. The patient should rest in bed, observe good general hygiene and receive a diet with a high vitamin and a high caloric content and a low residue. Iron and transfusions of blood should be given. Colonic irrigations are dangerous. Bargen's vaccine, autogenous vaccine and other vaccines are of doubtful value. Treatments with paratyphoid and antidysenteric serum, rectal injections of cod liver oil, administration of carotene in olive oil, of insulin, or of insufflation of estrogen, dry powder, and giving of histidine or bacteriophage all have their fervent advocates and equally violent critics. The influence of these forms of therapy on the death rate seems negligible. The mortality of the disease is estimated at from 30 to 50 per cent. Surgical intervention may have to be resorted to in order to save the life of the patient and limit the progress of the disease: Transverse ileostomy with complete external diversion of the fecal stream is recommended by David.

Ulcerative colitis occurred in a 3 month old child. The patient died with terminal pneumonia at the age of 5¾ months.

Book Reviews

Genital Abnormalities, Hermaphroditism and Adrenal Diseases. By Hugh Hampton Young, M.D. Price, $10. Pp. 649, with 534 illustrations (379 plates). Baltimore: Williams & Wilkins Company, 1937.

This book is a timely résumé of the problems suggested in the title. The embryologic factors concerning genital anomalies are stated in an easily understandable way. The possible action of sex-determining hormones on the fetus is postulated as a possible cause of these anomalies.

Plastic operations for each condition encountered are described. The original drawings by William P. Didusch serve to clarify some of the more involved surgical procedures.

Fifty-five case reports of hermaphroditism and pseudohermaphroditism are given, some of which cover a period of years. The difficulties of determining the sex of persons with these conditions are stressed, and Dr. Young gives in detail the various methods used. Several patients whose sex was diagnosed incorrectly are included, and the problems of environment and sexual life are reviewed.

The adrenal diseases and their effect on sex are illustrated by the case reports. Dr. Young has devised an operation for the bilateral exposure of both adrenal glands for the removal of tumors and hyperplastic growths.

The section on cryptorchidism and its treatment is of especial interest, since both the medical and the surgical treatment are discussed fully. A comparison is made between the effects of treatment and of nontreatment in such cases, with surprising results.

The relation of the various endocrine glands to the sex glands and to sexual characteristics is given in the closing chapter. The hypophysis and its action on the testicle, on the mammary glands and on sexual behavior are fully treated.

While the book covers a limited field in medicine and surgery, it is of great value for its vast amount of material. It is recommended to pediatricians and urologists who are responsible for the care of persons afflicted with the pathologic conditions discussed.

The Patient and the Weather. Volume IV, Part 2. By William F. Petersen, M.D., and Margaret E. Milliken, M.S. Price, $11. Pp. 729, with 380 illustrations. Ann Arbor: Edwards Brothers, Inc., 1937.

In this volume Dr. Petersen has again carried forward his study on the effect of weather on the human organism. The first section of the book, which discusses diseases of the thyroid, is the one most apt to convince the casual, skeptical reader that the observed bodily changes occur in response to changes in the weather and are not mere coincidences. The hypothyroid patient fails to respond. Given thyroid, however, he shows the characteristic development of the a. r. s. phase (anabolism, reduction and spasm) with sharp rises in barometric pressure. Both the hyperthyroid and the leptosomatic type at first respond quickly and effectively to atmospheric changes, but with repeated stimuli they reach the stage of exhaustion much more quickly than the normosomatic or the pyknic type.

Throughout the study of the other diseases discussed in this volume, diabetes, the blood dyscrasias and tuberculosis, one sees how definitely the ability of the organism to respond to the biologic demands occasioned by changes in the weather, reflects and determines the course of the disease. Exacerbations of the disease may occur with unusual atmospheric demands. If the exhaustion of the organism is too great, the normal response is delayed or absent. If the stimulus is of such magnitude that the biologic response required is impossible for the diseased organism, the episode may be fatal. Certainly an appreciation of these facts may many times prove of great value to the physician and to the patient.

Die Vitamine und ihre klinische Anwendung. By W. Stepp, J. Kühnau and H. Schroeder. Second edition. Price, paper, 8 marks; bound, 9.50 marks. Pp. 189. Stuttgart: Ferdinand Enke, 1937.

A textbook on a subject in which rapid advances are continually being made demands frequent revisions and additions. Beginning with a general discussion, the authors briefly give the history of the discovery of vitamins, define avitaminosis and hypovitaminosis and discuss the relation between vitamins, hormones and minerals. As yet the realm of hypervitaminosis is relatively unexplored.

Each of the known vitamins and some vitamins hypothesized for man are treated individually. The book describes the discovery of vitamins and early work done on them, their chemical structure, their physical and pharmacologic properties, if known, methods of determining their content in food, animals and man, the sources of supply of each, the effects of deficiency as noted experimentally and clinically and the effect of various diseases on their content in the body. The various vitamin-containing preparations on the market are described and compared, and the minimum and optimum dosages are given. Certain diseases which may be due to vitamin deficiency are discussed.

The subject matter is covered thoroughly, authorities for the statements being given in a complete bibliography after each chapter. Although some of the conclusions are highly speculative, the authors have presented them as such, together with the accepted material.

Die Bedeutung des Kuhmilchfettes für die Säuglingsernährung. Supplement to Archiv für Kinderheilkunde, No. 13. By Dr. Ernst Müller, with an introduction by Dr. E. Rominger. Price, 5 marks. Pp. 85, with 10 illustrations and 22 tables. Stuttgart: Ferdinand Enke, 1937.

This small volume presents a valuable summary of the results of the more recent investigations of the fat of cow's milk and interprets these with relation to infant feeding. An introductory chapter traces the history of the changing views on the value of this fat. The substance is now regarded as a biologically valuable factor in nutrition, and not simply as a fuel which can be replaced by other substances of equal caloric value, as it was formerly considered to be.

The chemical composition of the fat of cow's milk, including the vitamin and provitamin content, is fully discussed. The absorption and assimilation of the various chemical components and the significance of these factors for the metabolism of the infant are considered. In conclusion Dr. Müller discusses the practical application of our present knowledge of the characteristics of this substance.

It is interesting that, in a discussion of the vitamin D of cow's milk, the artificial enrichment of milk with vitamin D by feeding the cows irradiated yeast is mentioned but dismissed as impracticable, while irradiation of milk to increase its vitamin D content is not even mentioned.

Pediatric Urology. Volumes I and II. By Meredith F. Campbell, M.D., and John D. Lyttle, M.D. Price, $15 a set. Volume I, pp. 576; volume II, pp. 540; with over 1,350 illustrations. New York: The Macmillan Company, 1937.

The urology in these two volumes is presented by Dr. Campbell. It does not differ greatly in arrangement or presentation from that found in the standard textbooks on the subject. The general discussion does not differ from one on the urology of adults, except that data on children are included. The material is covered thoroughly, with particular reference to conditions met frequently by the pediatrician, such as infections, enuresis and anomalies of the genito-urinary tract. Diseases of the external genitals are discussed and pictured. A great deal of space is used in describing and picturing operative procedures.

Dr. Lyttle's contribution consists of about 45 pages on chronic interstitial nephritis. He gives a fine presentation of the accepted opinions on the nephritides, nephrosis and related conditions.

The subjects discussed by both authors are well covered, and both should be commended for their presentation of material. However, there is no doubt that

the two volumes will not be of use to the pediatrician, urologist or pediatric urologist, except for the part with which each specialist is immediately concerned.

Safely Through Childbirth, a Guide Book for the Expectant Mother. By A. J. Rongy, M.D. Price, $2. Pp. 192, with 20 illustrations. New York: Emerson Books, Inc., 1937.

Any book for the expectant mother must needs be written in such simple language that the true meaning of the complicated phenomenon of birth can be conveyed only with difficulty. The author has done well. Other physicians will take exception to many of his statements, especially those in regard to control of weight, cesarean section and reasons for perineal repair.

Dr. Rongy feels that it is the duty of the obstetrician to enlighten the patient gradually concerning the abnormal things which may occur during her confinement, so that she will be prepared for any eventuality. This information seems wholly uncalled for. A little knowledge is a dangerous thing. Why should pictures of abdominal incisions be included? The descriptions of various operative maneuvers seem entirely unnecessary in a book of this type. The discussion of so many abnormal conditions is far too alarming for a young mother to read; I wonder if the purpose of the book is not being defeated.

The efforts at "debunking" many of the popular misconceptions of the laity are admirable.

Les sérums de convalescents. By A. Stillmunkès. Price, 32 francs. Pp. 173, with 5 illustrations. Paris: Gaston Doin & Cie, 1937.

A book on convalescent serums seems particularly valuable at this time. An understanding of what can be expected from them and of the necessary precautions to be taken in preparing and administering them is certainly necessary. The author has had a great deal of experience with this type of therapy and of prevention, and he describes its development with unusual clearness.

Special chapters are given to a discussion of the use of convalescent serum in preventing and treating measles, scarlet fever, mumps, whooping cough and poliomyelitis. An interesting chapter gives particulars concerning the use of serum from a person who recently had been vaccinated successfully in the treatment of encephalitis associated with vaccination for smallpox. Another interesting point brought out concerns the use of convalescent serum in mumps. Here, serum must not be taken from a person who himself has been treated with convalescent serum, as the use of such serum seems definitely to increase the incidence of orchitis and meningitis.

The last two chapters are devoted to the technic of preparing and distributing convalescent serum.

The Development of Cardiac Enlargement in Disease of the Heart: A Radiological Study. By J. H. Palmer. Price, 1s. net. Pp. 48, with 58 illustrations. London: His Majesty's Stationery Office, 1937.

The development and progress of cardiac enlargement in disease of the heart were studied by direct superposition of successive cardiac outlines traced from teleroentgenograms. The conditions investigated were congestive failure, arteriosclerosis, hypertension, disorders of rhythm, myxedema, arteriovenous aneurysm and pericardial effusion. It is obvious that a consideration of cardiac enlargement under these headings is not altogether satisfactory, as several of the conditions might be operative in the individual case. In most instances a single case report serves to show the presence or absence of progressive cardiac enlargement in a given period. The total number of cases from which deductions are made is not given.

The author states that only broad conclusions have been drawn because of the small number of cases investigated. His monograph should stimulate further observations in this field.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Sept. 9-12, 1940.
American Committee:
Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Kenneth Blackfan, 300 Longwood Ave., Boston.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St., W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.
Place: Frankfort on the Main, Germany. Time: June 12-18, 1938.

FOREIGN

British Paediatric Association

President: Dr. J. Wilkie Scott, 40 The Rope Walk, Nottingham, England.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1, England.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen, Denmark.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen, Denmark.

Paediatrický Spolok na Slovensku

President: Dr. Pavel Radosa, Lazaretská 6, Bratislava, Czechoslovakia.
Secretary: Dr. S. Limbacher, Dlhá 2, Bratislava, Czechoslovakia.
Place: Pediatric Clinic, University, Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. T. Twistington Higgins, 12 Queen Anne St., London, W. 1, England.
Secretary: Dr. Harold Edwards, 57 Queen Anne St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv, Palestine.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv, Palestine.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Prof. Félix Hurtado Galtés, Carlos III 7, Habana, Cuba.
Secretary: Dr. Carlos Hernández Miyares, San Lazaro 370, Habana, Cuba.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Third Thursday of every month.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris.
Secretary: Dr. Jean Hallé, 10 bis rue du Pré aux Clercs, Paris.
Place: Hôpital des Enfants Malades, 49 rue de Sèvres, Paris. Time: 4:30 p. m., third Thursday of every month.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON DISEASES OF CHILDREN

Chairman: Dr. Clifford D. Sweet, 2940 Summit St., Oakland, Calif.
Secretary: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Place: San Francisco. Time: June 13-17, 1938.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Philip Van Ingen, 125 E. 71st St., New York.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Place: Del Monte Hotel, Del Monte, Calif. Time: June 9-11, 1938.
Region I. Place: Hotel Seneca, Rochester, N. Y. Time: Nov. 11-12, 1938.
Region II. Place: Skirven Hotel, Oklahoma City. Time: Nov. 16, 1938.
Region III. Place: Statler Hotel, Detroit, Mich., and Ann Arbor, Mich. Time: Oct. 27-29, 1938.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. Alton Goldbloom, 1543 Crescent St., Montreal, Quebec.
Secretary-Treasurer: Dr. Pearl Summerfeldt, Hospital for Sick Children, Toronto, Ont.
Place: Kingston, Ontario. Time: June 3-4, 1938.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Samuel Z. Levine, 525 E. 68th St., New York.
Secretary: Dr. A. A. Weech, 3975 Broadway, New York.
Place: The Berkshire Inn, Great Barrington, Mass. Time: Afternoon of May 4 and morning of May 5, 1938.

SECTIONAL

NORTH PACIFIC PEDIATRIC SOCIETY

President: Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Charles E. Conrad, 209-210 Professional Bldg., Harrisburg, Va.
Secretary: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.
Place: Oklahoma City. Time: Nov. 15-18, 1938.

STATE

Alabama Pediatric Society

President: Dr. J. H. Baumhauer, 56 St. Joseph St., Mobile.
Secretary-Treasurer: Dr. M. Vaun Adams, 803 Government St., Mobile.

Arkansas State Pediatric Association

Chairman: Dr. E. C. McMullen, 500 Main St., Pine Bluff.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.

California State Medical Society, Section on Pediatrics

Chairman: Dr. E. Earl Moody, 3780 Wilshire Blvd., Los Angeles.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.
Place: Pasadena. Time: May 9-12, 1938.

Florida State Pediatric Society

President: Dr. Douglas D. Martin, 442 W. Lafayette St., Tampa.
Secretary: Dr. Warren W. Quillian, 227 Avenue Aragon, Coral Gables.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. J. Harold Root, 103 N. Main St., Waterbury.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Indiana State Pediatric Society

President: Dr. Ernest R. Carlo, 2902 Fairfield Ave., Fort Wayne.
Secretary-Treasurer: Dr. Mathew Winters, 23 E. Ohio St., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Ruth Aleman, 1407 S. Carrollton Ave., New Orleans.
Secretary-Treasurer: Dr. Philip C. de Verges, 312 Audubon Bldg., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. John D. Craig, 33 E. 61st St., New York.
Secretary: Dr. Norman L. Hawkins, 11 Public Sq., Watertown.
Place: New York. Time: May 9-12, 1938.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John P. Scott, 1740 Bainbridge St., Philadelphia.
Secretary: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. C. R. Dengler, 131 W. Michigan Ave., Jackson.
Secretary: Dr. Ward Chadwick, 524 Medical Arts Bldg., Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by Society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. J. A. Henske, 1614 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. J. H. Murphy, 915 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. John LaBruce Ward, Arcade Bldg., Asheville.
Secretary: Dr. Lewis Elias, 36 Grove St., Asheville.

Oklahoma State Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

South Carolina Pediatric Society

President: Dr. Leland B. Salters, 317 S. Warley St., Florence.
Secretary-Treasurer: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.

Tennessee State Pediatric Society

President: Dr. Eugene Rosamond, 1074 Madison Ave., Memphis.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.

Texas Pediatric Society

President: Dr. John G. Young, 3930 McKinney Ave., Dallas.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Galveston. Time: May 10-12, 1938.

Virginia Pediatric Society

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.
Place: Danville, Va. Time: October 1938.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Claude L. Holland, 400 Locust Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, Weston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. William M. Champion, 2323 Prospect Ave., Cleveland.
Secretary: Dr. Arthur J. Horesh, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. T. B. Verner, 170 St. George St., Toronto.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto.

Bronx Pediatric Society

President: Dr. Samuel Tripler, 1555 Grand Concourse, New York.
Secretary: Dr. Harry S. Altman, 940 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Walter D. Ludlum, 1421 Cortelyou Rd., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank Vasder Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

Chicago Pediatric Society

President: Dr. C. A. Aldrich, 723 Elm St., Winnetka, Ill.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave., Chicago. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. W. H. Bradford, 1719 Pacific Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3622 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. W. J. Scott, 5140–2d Ave., Detroit.
Secretary: Dr. Harold E. Clark, 100 Atkinson Ave., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. T. F. Davenport, 104 Ponce de Leon Ave., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Walter F. Qualtrough, 920 Westheimer Ave., Houston, Texas.
Secretary-Treasurer: Dr. Allan Penny Bloxsom, 4402 Travis St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 1020 Boston Bldg., Salt Lake City, Utah.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

Kansas City (Missouri) Pediatric Society

President: Dr. W. R. Moore, 620 Francis St., St. Joseph, Mo.
Secretary: Dr. F. S. Hogue, 1103 Grand Ave., Kansas City, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Edwin F. Patton, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Henry F. Gallagher, 1930 Wilshire Blvd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Sidney D. Kramer, 61 Eastern Parkway, Brooklyn.
Secretary: Dr. Benjamin Stoleff, 1149 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: Third Wednesday of each month, October to May.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. Clyde V. Croswell, 1052 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. David W. Goltman, 1073 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. Joseph Shimpa, 2309 N. 36th St., Milwaukee.
Secretary: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Henry E. Utter, 122 Waterman St., Providence, R. I.
Secretary-Treasurer: Dr. Henry E. Gallup, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Samuel Z. Levine, 525 E. 68th St., New York.
Secretary: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Roger L. J. Kennedy, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Alternate months.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Julian M. Lyon, 40 Llanfair Rd., Ardmore, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

Richmond Pediatric Society

President: Dr. A. S. Hurt, 1028 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. Louise Fry Galvin, 2416 Stuart Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month (except July, August and September).

Rochester Pediatric Society

President: Dr. J. Merrel Parker, 11 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

Rocky Mountain Pediatric Society

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

St. Louis Pediatric Society

President: Dr. John Zahorsky, 536 N. Taylor Ave., St. Louis.
Secretary-Treasurer: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

Seattle Pediatric Society

President: Dr. Frank H. Douglass, Medical Dental Bldg., Seattle.
Secretary: Dr. C. Luverne Smith, Stimson Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Philip E. Rothman, 3875 Wilshire Blvd., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Damon O. Walthall, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. R. A. Higgons, 264 King St., Port Chester, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye, N. Y.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.

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